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INSULIN AND CEREBRAL DAMAGE

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Hypoglycemia manifests itself chiefly by symptoms due to disturbances of the autonomic and central nervous systems. In their monographs Sigwald [1] and Wilder [2] gave detailed descriptions of all neurologic and psychic symptoms to be noted during a hypoglycemic state, and it may be stated without hesitation that there is no neurologic or psychic abnormality which has not been observed either separately or in combination. Given susceptibility of the central nervous system to insulin, it is surprising that fatal damage of the central nervous system so seldom occurs in sufferers from diabetes treated with insulin. In 1932 Sigwald [1] gave short descriptions of 24 cases of fatal hypoglycemic coma known to him. In addition, Rathéry [3] reported a very instructive fatal case in 1938.

Fortunately, however, the fatal cases are rare. The hypoglycemic symptoms as a rule disappear when the blood sugar has been raised to the normal level through the administration of sugar. Sigwald and Wilder only incidentally mentioned disturbances persisting after the administration of sugar. Sigwald described a number of patients with chronic mental disturbances. During the last few years, moreover, various cases of serious, chronic disturbances of the brain have been reported, some of which ended in death.

The syndrome of hyperinsulinism is well known, especially through the reports of the American investigators (Harris; [4] Wilder; [5] Rynear-

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1. Sigwald, J.: L'hypoglycémie, Paris, Gaston Doin, 1932.

2. Wilder, J.: Klinik und Therapie der Zuckermangelkrankheit, Vienna, Verlag für Medizin, Weidmann & Co., 1936.

3. Rathéry, F.: Le diabete sucré: Leçons cliniques (1936-1937), Paris, J. B. Baillière et fils, 1938.

4. Harris, L.: The Diagnosis and Treatment of Hyperinsulinism, Ann. Int. Med. **10**:514, 1936.

5. Wilder, R. M.: Spontaneous Hypoglycemia, Internat. Clin. **46**:143, 1936.

son and Moersch,[6] and others). In 1938 Malamud and Grosh [7] published, in connection with a report on a patient suffering from pancreatic adenoma, an extensive survey of the literature on this syndrome. During that patient's life many psychic and neurologic symptoms were observed, and at autopsy extensive irregularities of the central nervous system were found.

The insulin shock therapy of Sakel has led to the observation of all kinds of cerebral complications. With this therapy the patient is brought into a deep coma. Usually the coma is interrupted after one to one and a half hours by peroral or intravenous administration of dextrose. Full consciousness is recovered as a rule within a half hour. There are numerous cases, however, as any one who applies this therapy will have experienced, in which consciousness does not return so soon. Here a distinction should be made between:

1. A delayed recovery of consciousness, during which, in addition to various forms of hyperkinesis, disturbances of speech and periods of exaltation, serious respiratory and pulse abnormalities may occur (Golden [8]).
2. A persistence of the comatose state, lasting from a few hours to several days, after which consciousness gradually returns (Salm [9]). Not seldom many weeks or even months may elapse before the neurologic and psychic symptoms may be said to have totally disappeared. Plattner [10] and Milch and Bolles [11] described a case in which Korsakoff's syndrome occurred and persisted for several months. Pap,[12] who as early as 1936 gave an excellent description of the syndrome of Sakel's insulin treatment, described in detail 2 cases of prolonged coma, in the course of and following

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6. Rynearson, E. H., and Moersch, F. P.: Neurologic Manifestations of Hyperinsulinism and Other Hypoglycemic States, J. A. M. A. **103**:1196 (Oct. 20) 1934. Carlson, L. A., and Rynearson, E. H.: An Unusual Case of Spontaneous Hypoglycemia, Proc. Staff Meet., Mayo Clin. **12**:486, 1937. Rynearson, E. H., and Walters, W.: An Unusual Case of Spontaneous Hypoglycemia, ibid. **13**:728, 1938.

7. Malamud, N., and Grosh, L. C., Jr.: Hyperinsulinism and Cerebral Changes: Report of Case Due to Islet Cell Adenoma of Pancreas, Arch. Int. Med. **61**:579 (April) 1938.

8. Golden, L. A.: Neurologic Manifestations in "Hypoglycemic Shock" (Sakel), Ann. Int. Med. **11**:819, 1937.

9. Salm, H.: Benommenheitszustände im Anschluss an die Insulinshockbehandlung von Schizophrenen, München. med. Wchnschr. **84**:1046, 1937.

10. Plattner, P.: Amnestisches Syndrom nach Insulin-Cardiazol-Behandlung, Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:728, 1938.

11. Milch, E. C., and Bolles, M. M.: A Case of Prolonged Coma Following Insulin with Eventual Recovery, J. Nerv. & Ment. Dis. **88**:817, 1938.

12. Pap, Z.: Erfahrungen mit der Insulinshocktherapie bei Schizophrenie, Monatschr. f. Psychiat. u. Neurol. **94**:318, 1936.

which serious disturbances of the pyramidal and extrapyramidal tracts, cramps and motor aphasia, combined with abnormalities of temperature, pulse and respiration, were noted. After administration of dextrose the different symptoms in all their variety may be observed just as prior to the onset of the comatose state. Not always, however, is there a total recovery. Schraagen [13] observed chronic disturbances of the brain.

3. An uninterrupted coma followed by death after a shorter or longer period (Müller [14]; Leppien and Peters [15]; Salm [9]; Timmer [16]; Kastein; [17] Cammermeyer; [18] MacKeith and Meyer [19]). Although in some cases (an instance was observed by us but is not commented on in this report) extensive pulmonary and other abnormalities have been found at autopsy, the existence of a serious disturbance in the functions of the central nervous system is here absolutely undeniable.

During the last few years cases have been reported of permanent damage of the brain in patients suffering from severe diabetes who required large doses of insulin and in whom a continuous appearance of hypoglycemic symptoms could not be avoided. The syndromes in these patients bear a close resemblance to those seen after prolonged coma in patients given Sakel's therapy.

Fenz and Kogerer [20] described the case of a 16 year old boy who had suffered from serious diabetes from his fourth year onward and who during the last fifteen years frequently had hypoglycemic symptoms. He was given 100 units of insulin per day. Dulness and obliviousness had been observed for five months when he was admitted to the hospital in a serious hypoglycemic coma with many epileptic seizures. After he recovered consciousness the patient showed for a fortnight a syndrome

13. Schraagen, J. C.: Case of Dementia Developing After Insulin Shock Therapy of Schizophrenia, Psychiat. en neurol. bl. **42**:373, 1938.

14. Müller, M.: Die Insulintherapie der Schizophrenie, Schweiz. Arch. f. Neurol. u. Psychiat. (supp.) **39**:9, 1937.

15. Leppien, R., and Peters, G.: Todesfall infolge Insulinshockbehandlung bei einem Schizophrenen, Ztschr. f. d. ges. Neurol. u. Psychiat. **160**:444, 1937.

16. Timmer, A. P.: Death During Treatment of Schizophrenic Patient with Insulin Shock According to Sakel Method, Nederl. tijdschr. v. geneesk. **82**:3088, 1938.

17. Kastein, G. W.: Insulinvergiftung: I. Klinische und pathophysiologische Beschreibung, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:322, 1938.

18. Cammermeyer, J.: Ueber Gehirnveränderungen, entstanden unter Sakelscher Insulintherapie bei einem Schizophrenen, Ztschr. f. d. ges. Neurol. u. Psychiat. **163**:617, 1938.

19. MacKeith, S. A., and Meyer, A.: A Death During Insulin Treatment of Schizophrenia, with Pathological Report, J. Ment. Sc. **85**:96, 1939.

20. Fenz, E., and Kogerer, H.: Hypoglykämie und Schizophrenie, Jahrb. f. Psychiat. u. Neurol. **54**:241, 1937.

characterized by negativism, catalepsy, grimacing and motor restlessness. Subsequently improvement gradually set in; after four months, however, apathy and dulness still persisted.

Helland-Hansen [21] described the case of a woman aged 33 who had been suffering for eight years from severe diabetes and who was given 212 units of insulin daily. While she was in a hypoglycemic coma, mistaken by the family doctor for hyperglycemia, she was given 160 units of insulin subcutaneously and 160 units intramuscularly. The coma persisted for three days, during which Cheyne-Stokes respiration, clonic cramps and reflex changes were observed. Then for nine days there existed a dream state, with symptoms of parkinsonism, tremor, perspiration, a masklike face and slowness of thought. Later improvement occurred, but after seven months the patient was still an invalid and had to be accompanied when going out. Labbé and Boulin [22] described a case characterized principally by neurologic irregularities. They observed a patient 33 years of age who in addition to hypoglycemic coma presented hemiplegia and aphasia of the right side. Aphasia was still present after two months. They believed they were justified in definitely excluding a primary vascular disturbance.

Also, in diabetic patients treated with protamine zinc insulin, the hypoglycemic symptoms, once they have occurred, have not seldom been seen to disappear only after some hours or sometimes only after some days, in spite of the fact that the blood sugar has been at normal levels for some time. In these cases it should be assumed that the protamine zinc insulin had an unfavorable influence on the central nervous system. The fact that protamine zinc insulin can keep the blood sugar at abnormally low levels for many hours points to a danger for the central nervous system. The already rather high percentage of patients treated with protamine zinc insulin who have died of hypoglycemia points in the same direction.[23]

We shall now report 2 cases of serious damage to the brain. The first case was that of a schizophrenic patient in whom a complication occurred during administration of the therapy of Sakel; the second was that of a psychically sound diabetic patient treated with regular and protamine zinc insulin who remained in a comatose state for many days.

21. Helland-Hansen, B.: Psychose nach Insulinvergiftung, Norsk mag. f. lægevidensk. **98**:1306, 1937.

22. Labbé, M., and Boulin, R.: Les accidents hémiplégiques au cours de l'insulinothérapie, Presse méd. **45**:225, 1937.

23. Danger of Protamine Insulins, editorial, J. A. M. A. **111**:254 (July 16) 1938. Wilder, R. M.: Disease of Metabolism and Nutrition: A Review of Certain Recent Contributions, Arch. Int. Med. **59**:329 (Feb.) 1937. Boller, R., and Pilgerstorfer, W.: Die Hypoglykämie bei Protamin-Zink-Insulinanwendung, Klin. Wchnschr. **17**:1065, 1938. Groen, J., and Garrer, A. H.: Death Due to Hypoglycemia During Treatment with Protamine Zinc Insulin, Nederl. tijdschr. v. geneesk. **83**:1844, 1939.

Although the blood sugar of the diabetic patient had not been determined during the initial days of the coma, the syndrome resembled that of the schizophrenic patient, as well as the syndromes observed in other patients described in the literature on the subject, to such an extent that we believe we may confidently call the case an instance of hypoglycemic damage to the brain.

REPORT OF CASES

Case 1.—K. Z., a man aged 25, a German refugee and merchant's apprentice, was admitted to the sanatorium March 7, 1938. He refused to learn a trade and gave as a motive that he was a great singer. During the first months of 1938 he voiced paranoid ideas, viz., that he was forced to marry against his will; that at night he was narcotized; that his fillings were being pulled from his teeth; that he was being poisoned with anthracite put in his cocoa. In the street he exposed himself, thinking "they" wanted to turn him into a girl. On admission to the sanatorium his behavior was theatrical; he suddenly cried out, thinking that he was being murdered. He was strongly cataleptic and gave way to senseless screaming fits and catatonic states of agitation. On physical examination, including studies of the blood, urine and cerebrospinal fluid, no abnormalities were found. Wassermann tests of the blood and cerebrospinal fluid were negative. His condition was diagnosed as schizophrenia.

In April 1938 Sakel's insulin shock treatment was started. On the fifth day of treatment coma set in, on the administration of 80 units of insulin. By the twenty-fourth day of treatment the patient had been in coma seventeen times. Prior to becoming comatose he was always very restless; while comatose he had tonic cramps. The coma on the twenty-fifth day of treatment, after 90 units had been administered, resembled the previous ones, but the patient did not recover consciousness after oral administration of dextrose. Neither intravenous administration of dextrose nor injection of epinephrine hydrochloride gave a better result, although the level of the blood sugar was raised to 220 mg. per hundred cubic centimeters. Lumbar puncture did not produce improvement either. The temperature was 40.8 C. (105.4 F.); the pulse rate, 200. Electrocardiographic examination revealed sinus tachycardia. The blood pressure was 140 systolic and 70 diastolic; the respirations were 46 per minute and fairly regular. There were occasional myoclonic spasms in the face and there were movements of the arms and legs. Babinski's sign was present on the right side; tendon reflexes were present. The therapy consisted in intravenous injection of 200 mg. of theophyllineethylenediamine. The comatose state still persisted. The corneal and pupillary reflexes were present. In the evening he was calmer: the pulse rate was 140 and the temperature 39.7 C. (103.4 F.)

The next day, May 26, the condition remained the same. The pulse rate was 120 and the temperature was 38.8 C. (101.8 F.); the respiratory rate was 28. There were constant slight myoclonic spasms and swinging movements of the limbs. The tendon reflexes were normal. The abdominal and cremasteric reflexes were absent. There were no signs of meningeal irritation. Babinski's sign was present on the right side. No obvious abnormalities of the fundus oculi were observed. The cerebrospinal fluid was normal. The sugar metabolism was disturbed. There was sugar in the urine, with albumin and casts. The therapy consisted in intravenous administration of a hypertonic solution of sodium chloride. The patient was fed by an oral tube a diet rich in vitamin B complex. On May 27 the comatose state was a little less profound; there was a reaction on pain stimulation, and Babinski's sign had disappeared. Herpes labialis developed. On May 28 the patient was somnolent.

When his name was called, he hardly woke up. Feeding was no longer artificial. There was a lowering of the temperature. On May 29 ptosis of the left eye appeared, also strabismus and somnolence. Clinically there was a great resemblance to the syndrome of severe encephalitis. The therapy consisted in intravenous injection of a 40 per cent solution of methenamine. On May 31 the more consciousness returned the greater his restlessness became. There were typical rolling movements along the body axis, accompanied by digging of the head into the pillows and swinging movements of the limbs. The condition bore slight resemblance to chorea. There was continuous salivation. He obviously could not pronounce a single word, but he uttered some unintelligible sounds.

On June 8 he had fits of crying and many symptoms of Parkinson's syndrome. The forearms were rigidly flexed and the head bent, alternated by ballistic and rolling movements of the body. Salivation continued; ptosis disappeared; the cremasteric reflexes returned; the abdominal reflexes were still absent. His behavior was noncooperative. On June 10 the patient uttered a few words. In bed he

TABLE 1.—*Laboratory Data of the Urine and Blood (Case 1)*

Date	Albumin	Reaction	Sediment	Blood Sugar: Sugar, %	Blood Sugar: Mg. in 100 Cc.	Blood Sugar: Hour	Comment
5/25/38	....	.....	.....	....	223	3 p.m.	After intravenous injection of dextrose
					81	5 p.m.	
5/26/38	++	Acid	Some erythrocytes, some leukocytes, many hyaline casts	1.8	154	10 a.m.	
5/27/38	1 °/oo*	Alkaline	Some erythrocytes	0.75	192	5 p.m.	
5/28/38	1 °/oo	Acid	Some hyaline and some granular casts	2.5	...	.....	
5/29/38	¾ °/oo	Alkaline	Three leukocytes	2.5	...	.....	Only a few urine specimens could be examined
5/30/38	½ °/oo	Alkaline	Some casts	0.7	114 before eating		
6/ 3/38	....	.....	.....	....	113 before eating		
6/10/38	Trace	Alkaline	.....	....	101 before eating		
6/20/38	....	Alkaline	.....	....	70 before eating		

* °/oo indicates parts or grams per thousand or per liter.

always had the same typical rolling and swinging movements. Sucking and biting reflexes appeared as soon as any object was made to touch his mouth. He could not take food without assistance. On June 20 he pronounced his name and was able to tell time by his watch. There remained persistent incontinence of feces and urine. On June 23 his walking was ataxic; he could not write or read, showed paraphasia, motor and sensory aphasia and slept much. On June 28 he had echolalia, no notion of time and place and a disturbed memory. Polyphagia developed. He ate whatever was put before him, even tobacco, grass and wood wool. Sucking and biting reflexes were present, and the abdominal reflexes returned.

On July 7 psychologic examination revealed motor and sensory aphasia, agraphia, tactile agnosia, alexia and extreme amnesia. The higher psychic functions had disappeared. Only a few strongly automatized fragments of former knowledge were still present.

On August 12 he had persistent alexia; his memory improved and the aphasia disappeared. The motor functions were slightly disturbed. His behavior was infantile, with faulty speech and permanent masturbation.

On September 17, the intellectual level, experimentally ascertained, was that of a child of 8.

On April 16, 1939, the greater part of the motor functions had been recovered. Alexia, which of all disturbances had been the most severe and the most persistent, had now disappeared. The intellectual functions appeared experimentally to have been, for the most part, recovered. Relative to the period from February to September 1938 there was total amnesia. Remnants of megalomania could still be observed, as well as disturbances of judgment. The infantile behavior persisted. Roentgenograms of the skull were normal.

Laboratory Data.—In table 1 a number of data from examinations of the urine and blood have been combined. During the first days there was a disturbance of the sugar metabolism, i. e., hyperglycemia and glycosuria. This disturbance soon disappeared, however, and made way for a contrasting picture, viz., a

TABLE 2.—*Laboratory Data on the Blood (Cases 1 and 2)*

Date, 1938	Plasma Chlorides as Sodium Chloride, Mg. in 100 Cc.	Nonprotein Nitrogen, Mg. in 100 Cc.	Corpuscular Volume, %	Cholesterol, Gm. per 100 Cc.	White Blood Cells: Total	Eosinophils	Basophils	Nonsegmented	Segmented	Lymphocytes	Monocytes	Sedimentation Rate	Fibrinogen
Case 1													
5/25	582	38	50.9	...	17,000	..	..	2	86	12	..	..	.....
5/26	553	..	....	...	16,300	..	..	..	..	..	..	..	.....
5/27	588*	40	....	...	.....	..	..	8	49	37	6	..	.....
5/28	...	..	....	...	13,600	3	1	3	54	37	2	..	.....
5/30	564	31	48.4	...	8,600	1	1	5	38	50	5	..	.....
6/ 2	...	..	....	...	13,100	2	1	3	58	34	2	64	6 ‰
6/ 9	571	26	49.3	160	9,900	..	..	..	..	..	..	48	.....
6/16	...	..	....	...	10,600	2	1	2	44	44	7	..	.....
6/27	567	..	....	...	9,400	1	..	3	43	49	4	16	3.5 ‰
7/ 4	560	24	47.1	320	7,100	5	..	..	44	50	1	8	.....
9/ 5	589	..	....	250	5,300	3	..	1	62	33	1	5	.....
Case 2													
2/16	...	..	....	...	.....	1	1	3	54	38	3	5	.....
6/15	...	Urea, 100	....	...	.....	..	..	..	..	..	..	..	.....
6/18	...	..	....	...	8,600	..	..	8	77	7	8	20	.....
7/19	...	..	....	...	5,800	2	..	3	63	29	3	9	.....
7/24	555	Urea, 56	52.7	280	6,500	2	..	1	69	27	1	6	3 ‰
8/17	563	Nonprotein Nitrogen, 23	54.7	...	4,900	..	..	..	..	..	..	..	.....
10/20	580	Urea, 31	51.5	...	5,000	2	..	4	69	22	3	..	.....

* During treatment with sodium chloride.

low sugar content and only a slight increase after administration of 100 Gm. of dextrose. For instance, the blood sugar curve taken on July 4 showed the following values: 68 mg. per hundred cubic centimeters before 100 Gm. of dextrose was administered; at one-half hour after the administration of dextrose, 119 mg.; at one hour, 107 mg.; at one and one-half hours, 98 mg.; at two hours, 56 mg.; at three hours, 80 mg.; at four hours, 84 mg., and at five hours, 89 mg. This curve was determined during a period in which the patient ate and drank a good deal, eating often as much as sixteen slices of bread in the morning and voiding 2½ liters of urine on an average. The cholesterol content of the blood increased from 160 mg. per hundred cubic centimeters on June 9 to 320 mg. on July 4. The laboratory data on the blood have been summarized in table 2. During the first week there was a slight increase in the nonprotein nitrogen content. The chloride content was constantly fairly low. During the comatose state there was a rather marked leukocytosis, with lymphopenia and an absence of monocytes on the first day and with an increase of nonsegmented neutrophils and lymphocytosis with 6 per cent monocytes on the third day; eosinophil cells were not observed before the

fourth day. The number of leukocytes decreased to normal in the month of June. Lymphocytosis persisted. The initial strongly increased rate of sedimentation of the erythrocytes also gradually subsided to normal. With few exceptions, repeated examination of the spinal fluid (table 3) showed normal values. The blood pressure, which had not been taken on the first day, still showed an increase on the second day, 230 mm.; later it subsided to normal. The chloride content on the first day was high, 783 mg. of sodium chloride per hundred cubic centimeters. This certainly was abnormal in proportion to the chloride content of the blood plasma, 582 mg. of sodium chloride per hundred cubic centimeters. The lumbar puncture was made fifteen minutes after taking the blood pressure.

Summary.—A patient who was being treated for schizophrenia with insulin was not awakened from the coma produced by administering 90 units of the drug, notwithstanding a copious supply of sugar and a

TABLE 3.—*Laboratory Data on the Cerebrospinal Fluid (Cases 1 and 2)*

Date, 1938	Appearance	Cells per 3 Cu. Mm.	Protein, Mg. in 100 Cc.			Non-protein Nitrogen, Mg. in 100 Cc.	Chlorides as Sodium Chloride, Mg. in 100 Cc.	Initial Pressure, Mm.	Sugar, Mg. in 100 Cc.
			Total	Albumin	Globulin				
Case 1									
3/24	Clear	13	25.7	22.8	2.9	Colloidal gold and mastic reactions normal			
5/25	Clear	13	17.4	14.5	2.9	17	783	...	55
5/26	Clear	..	....	....	....	21	791*	230	115
5/28	Clear	..	13	11.6	1.4	Colloidal gold and mastic reactions normal			125
5/29	Clear	3	14.5	13.1	1.4	23	741	150	...
6/ 9	Clear	2	....	....	....	14	735	...	...
Case 2									
6/16	Clear	6	30.4	....	....	Colloidal gold and mastic reactions normal		200	...
6/23	Clear	7	33.4	20.3	13.1	..	...	180	...
7/28	Clear	8	30.4	15.9	14.5	..	732	120	...
8/29	Clear	2	18.8	14.5	4.3	15	702	...	...

* After intravenous injection of sodium chloride.

normal blood sugar content. After three days of coma, consciousness gradually returned. In addition to fever, tachycardia and tachypnea, extensive neurologic and psychic symptoms were recorded which persisted for many months.

CASE 2.—A laundryman now 22 years of age entered Juliana Hospital, Apeldoorn, in a state of coma on July 15, 1938. During April 1936 he had been nursed in the same hospital on account of a pelvic and left femoral fracture sustained in a motorcar accident. On that occasion he had not been unconscious. In the past he had always been healthy. Thirteen days after the accident the patient started drinking great quantities of water and urinating much and frequently. No dextrose was found in the urine during the first five days after the accident. On the thirteenth day, however, 200 Gm. of dextrose was excreted. With the patient on a regimen of 15 and 10 units of regular insulin the urine could easily be freed from dextrose. In July the patient started working again.

In March 1937 he entered the medical department of the Utrecht University Clinic (Prof. Hymans v. d. Bergh) as for the last few months he had been very thirsty again and had excreted a high percentage of dextrose in the urine. It

appeared very difficult to regulate his sugar metabolism. While on the one hand the blood sugar rose very quickly after the injection of carbohydrate without insulin and the blood sugar during fasting was very high, often as much as 500 mg. per hundred cubic centimeters, on the other hand there existed a great sensitivity to insulin. Several times there were hypoglycemic manifestations. After five months the patient left the clinic on a diet of 160 Gm. of carbohydrate and 30, 10 and 25 units of insulin per day.

In the middle of February 1938 he reentered the clinic on account of emaciation and increasing glycosuria. The administration of protamine zinc insulin was instituted at once. It appeared possible to control his sugar metabolism satisfactorily with 40 units of protamine zinc insulin in the morning and 20 units of unmodified insulin in the afternoon. The excretion of sugar ranged from 0 to 40 Gm. of dextrose per day. He left the clinic on April 23 and returned to work.

On Sunday morning, June 12 the patient took his insulin as usual at 7:30. His family did not notice anything unusual. He told them he was going back to bed but that he would come down to breakfast in half an hour. He did not reappear, however, and his family found him lying against his bed, dazed and sleepy. He still uttered some words to the effect of wanting to eat his porridge, but he became more and more dazed. A physician was sent for. On the latter's arrival the patient was in a subcomatose state. He did not perspire; his mouth secreted a mucous fluid. The physician injected 60 units of insulin. Total coma set in, which lasted for many days. On the evening of June 12 the physician injected 40 units of protamine zinc insulin; the next day he injected 20 units supplemented by 40 units of unmodified insulin, and, as acetone (no dextrose) was found in the urine, he administered sodium bicarbonate and dextrose per rectum. No other food was given. The next day the physician again administered 20 and 40 units of insulin, 3.5 Gm. of sugar per hundred cubic centimeters having been found in the urine at the time. The following day he gave the patient 20 units of insulin twice. On admission to Juliana Hospital that night the patient was in deep coma. Examination by Dr. Rodbard, director of the hospital, revealed that his pulse and respirations were normal; there was no question either of Kussmaul's or of Cheyne-Stokes respiration. The skin was dry, with many spots of decubitus. The tonus of the bulbus oculi was normal and the tonus of the muscles of the extremities was lowered. The patient did not react to pain stimulation. The reflexes of the corneas and pupils were present. Around the mouth there were, as usual in hypoglycemic states, peculiar fibrillary contractions. There were no signs of meningeal irritation and no abnormalities of the lungs and heart. The abdomen was sunken, and the abdominal reflexes were absent. The reflexes of the lower extremities were weak; Babinski's sign was present on both sides. The temperature mounted to 37.8 C. (100 F.), the blood sugar to 320 mg. and urea to 100 mg. per hundred cubic centimeters. The urine revealed 5 per cent dextrose; the test for acetone was positive; that for diacetic acid was negative. The test for albumin was slightly positive. The patient was incontinent of feces and urine. The treatment consisted in intravenous injection of sugar, administration of insulin and hypodermoclysis of physiologic solution of sodium chloride.

The next day the coma was a little less profound; the patient was rather restless and made choreatic and athetosic movements with his arms. The fundus oculi was normal and the cerebrospinal fluid was clear and almost normal. During the following days a slight improvement was observed. The patient reacted on pain stimulation; he made sucking movements when the corners of his mouth were touched with a finger, and he swallowed liquid poured into his mouth.

Toward the end of June he became a little more lively, but otherwise his condition remained the same. He behaved like a complete idiot. He did not talk but continuously uttered bestial sounds. Thus it became necessary to send him to the asylum for patients with mental disease, Apeldoornsche Bosch. He stared vacantly, did not take any notice of his surroundings, did not react on being called and did not follow either light or people. He slobbered and made continual gnawing movements; he ate greedily, gnawed at the bedside and continued to be incontinent of feces and urine. This condition has continued up to the time of writing; there is only very slight improvement. At present the patient follows people who walk around his bed, but he does not recognize food when

TABLE 4.—*Blood Picture During Induced Hypoglycemia*

Date	Hour	Total		Percentages						Blood Sugar, Mg. per 100 Cc.
		Leukocytes	Eosinophils *	Eosinophils	Basophils	Nonsegmented	Segmented	Lymphocytes	Monocytes	
Patient A, ♂, 27 yr. old										
11/23/38	7:30 a.m. Before injection of 340 units insulin	6,900	600	2	1	2	58	34	3	99
	10:30 a.m. Precoma	9,300	200	0	0	2	71	26	1	55
	12:30 a.m. Coma	14,600	50	0	0	6	78	16	0	41
	5:30 p.m. 4 hours after the end of coma	12,000	200	0	0	1	59	38	2	112
11/24/38	7:30 a.m.	8,400	400	5	0	1	64	26	4	102
Patient B, ♀, 23 yr. old										
12/ 5/38	7:30 a.m. Before injection of 320 units insulin	10,400	500	5	0	2	54	35	4	
	1:00 p.m. Coma	28,100	3†	0	1	3	89	5	2	
	6:00 p.m. 4 hours after the end of the coma	10,600	6†	1	0	3	78	17	1	
12/ 6/38	7:30 a.m.	11,300	400	4	2	2	56	33	3	
Patient C, ♂, 32 yr. old										
10/14/38	7:30 a.m. Before injection of 220 units insulin	4,400	500	12	0	0	50	36	2	
	11:30 a.m. Coma	13,200	50	1	0	2	81	15	1	
	4:30 p.m. 4 hours after the end of coma	9,600	100	2	1	2	74	20	1	
10/16/38	8:30 a.m.	4,600	600	6	1	1	30	60	2	

* Method of Friedman (J. A. M. A. **103**: 1618 [Nov. 24] 1934).
† Total in counting chamber.

it is held before his eyes. He can walk, however, in a very ataxic manner. The reflexes of his abdomen have returned, and the positive Babinski and Chaddock signs on the left, which persisted longest, have disappeared, as have the sucking reflexes. But another serious symptom has manifested itself: The patient suffers regularly from epileptic convulsions, sometimes of the jacksonian variety, alternately beginning on the right and on the left side.

Often, on account of such an epileptic state, it has become necessary to administer somnifen (a mixture of the diethylamine salts of diethylbarbituric acid and allylisopropylbarbituric acid) intravenously. However, a roentgenogram of the skull revealed no abnormalities. The controlling of the sugar metabolism of this patient, who still is very sensitive to insulin and whose blood sugar rises quickly without insulin, has caused new difficulties. He repeatedly refuses food after having received an injection of insulin a moment before. Often he vomits what he has been fed artificially, especially during the days following convulsive

seizures. All sorts of neurologic irregularities have developed, and a number of times Cheyne-Stokes respiration for a long period. A correlation between the lowering of the blood sugar and the convulsive seizures could never be proved, however. The question that remains to be answered is why the patient lapsed into coma on June 12. We believe that the blood sugar values during fasting in the month of April may give an explanation. While in the first five days of April the values amounted to 300, 262, 346, 344 and 170 mg. per hundred cubic centimeters, these figures were 185, 91, 226, 110 and 106 mg. per hundred cubic centimeters in the last days before the patient left the hospital, a curve which is considerably lower. The tendency toward a lowering of the blood sugar still persisted after his dismissal from the hospital, until at last hypoglycemic symptoms manifested themselves.

Laboratory Data.—Results of examinations of the blood and of the spinal fluid are summarized in tables 2 and 3. As the patient received little liquid during the first three days of coma, the urea content of the blood was increased to 100 mg. per hundred cubic centimeters. After the administration of liquid the urea content decreased rapidly. It is true that the hematocrit value remained slightly increased. This was due to polyuria. There was constant excretion of sugar. This also accounts for the low chloride values. On the sixth day the blood, with a normal quantity of leukocytes, showed a shift to the left, 8 per cent of the cells being monocytes, without any eosinophil cells. In the spinal fluid a slight increase in cells and globulin was revealed, which disappeared after three months. The Wassermann reactions of the blood and spinal fluid were negative.

Summary.—A diabetic patient treated with regular and protamine zinc insulin was found in a comatose state and was given another 60 units of regular insulin. The coma persisted for six days, after which several functions were gradually recovered, viz., eating, laughing, crying, emitting inarticulate sounds, defense against pain stimulation and, finally, standing up and ataxic walking. All signs of rational thinking, higher feelings and reasoned actions remained absent. Briefly, the intellectual level finally reached by the patient was that of a complete idiot. The entire mental picture became that of an animal.

COMMENT

The symptoms occurring in both patients were strikingly similar. During the comatose state there were myoclonic spasms in the face and movements of the upper extremities similar to those of patients with chorea and athetosis. Of the neurologic disturbances, Babinski's sign and the absence of the abdominal reflexes persisted longest. In both patients sucking and biting reflexes, as well as polyphagia and salivation, occurred. The spinal fluid contained nothing abnormal. The irregularities in the first patient were of a passing nature, whereas those in the second were serious and chronic. At this point we may elaborate a few of the irregularities observed:

1. The postcoma disturbance of the sugar metabolism in case 1 has been described also by Kastein.[17] Lups [24] observed that the longer the

24. Lups, S.: Glucosurie nach Insulinkoma, Klin. Wchnschr. **17**:207, 1938.

coma ensuing from Sakel's insulin therapy is allowed to continue the more the glycosuria occurring after administration of an equal amount of dextrose increases. It was his opinion that this is due to a disturbance of the liver. In our opinion, however, the cause should be sought for in a cerebral disturbance.

2. In case 1 fairly marked albuminuria was found during one week; in case 2 only a slight trace of albumin could be observed in the urine.

3. The very extended occurrence of herpes labialis in case 1 must be mentioned separately. Pap[12] reported this symptom in one of his patients.

4. In both cases, during the coma the blood picture presented a shift to the left with absence of eosinophils, and in the first case, leukocytosis as well. A similar blood picture has been noted in other cases of induced hypoglycemia, but only for a short time, during the coma and a few hours after consciousness had been fully restored through the administration of dextrose (table 4). In the case studied by Malamud and Grosh,[7] too, no eosinophil cells were observed during a serious hypoglycemic state.

SUMMARY AND CONCLUSIONS

A schizophrenic patient in whom coma was produced by the administration of 90 units of insulin recovered consciousness only after three days, in spite of a normal and even increased content of sugar in his blood. During this period and following it there occurred, in addition to neurologic and psychic symptoms, irregularities in the sugar and water systems, also initially a high temperature, tachycardia and tachypnea. Most of these symptoms disappeared after one year.

A diabetic patient without psychic abnormalities, who was treated with regular and protamine zinc insulin, became comatose and was given 60 units of insulin. After a coma of six days a slight improvement took place. Extensive neurologic disturbances were observed. The intellectual level reached by the patient was that of a complete idiot. Because of the great similarity in the symptoms of the two patients it is our contention that cerebral damage caused by insulin-induced hypoglycemia must be assumed to have occurred in the second patient as well, in spite of the lack of data on the blood sugar values during the first days of the comatose state.

Thus, the danger to the brain ensuing from Sakel's technic and from the treatment of diabetic patients with insulin and protamine zinc insulin should not be underestimated.

Prof. de Langen, Dr. Kulst, Dr. Rodbard and Dr. Simons provided the details from the clinical records in case 2.

DISSECTING ANEURYSM OF THE AORTA

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It is stated in the 1928 edition of Osler and McCrae's textbook [1] that "dissecting aneurysm is uncommon. There were only two cases in sixteen years at the Hopkins' Hospital where aneurysm is exceptionally frequent." Professor Shennan, in a monograph,[2] reviewed all the reports in the literature up to 1934 and accepted 297 cases, including his own, as instances of true dissecting aneurysm of the aorta.

In the American literature since 1932 at least 65 cases have been reported. Hamburger and Ferris [3] reported 6 cases in which the condition was discovered at autopsy; all 6 cases were observed within the short period of seven months, while in the preceding nine years only 10 cases had come to necropsy at the Cincinnati General Hospital. The incidence noted by other authors [4] has been 1 case of dissecting aneurysm in 300 to 500 autopsies. The 4 cases described in this report were observed in the course of a year, during which time about 180 autopsies were performed and approximately 2,000 patients were treated in the hospital. Such a high incidence is undoubtedly fortuitous, but it is obvious that the dissecting type of aneurysm is not so uncommon and that the recognition of the condition is of practical as well as academic importance.

I report 4 cases of dissecting aneurysm, proved to be such at autopsy. Two of these will be described in some detail because the patients lived a considerable length of time (93 days and 14 months, respectively) after the onset of their illness. In one of these the diagnosis was made before

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From the Cardiovascular Unit, Veterans' Administration, Washington, D. C.

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1. Osler, W., and McCrae, T.: The Principles and Practice of Medicine, New York, D. Appleton and Company, 1928.

2. Shennan, T.: Dissecting Aneurysms, Medical Research Council, Special Report Series, no. 193, London, His Majesty's Stationery Office, 1934.

3. Hamburger, M., Jr., and Ferris, E. B., Jr.: Dissecting Aneurysm, Am. Heart J. **16**:1 (July) 1938.

4. (*a*) Glendy, R. E.; Castleman, B., and White, P. D.: Dissecting Aneurysm of the Aorta, Am. Heart J. **13**:129, 1937. (*b*) Weiss, S.: Clinical Course of Dissecting Aneurysm of Aorta, M. Clin. North America **18**:1117, 1935.

death (case 1). Of the patients, 3 were white and 1 was Negro. Their ages ranged from 39 to 50 years, with an average of 44 years. There was no evidence of syphilis in the history, serologic reactions or results of examination of any of these patients.

REPORT OF CASES

CASE 1.—A. J. M., a Negro aged 41, who had had no significant illnesses except pneumonia five years previously and who had been in good health until the presenting illness, was admitted to the hospital of the Veterans' Administration on Dec. 14, 1936. He had never been told that his blood pressure was high, and nothing in his history suggested the presence of significant hypertension.

He stated that after an evening meal, several days before his admission to the hospital, he suddenly had become nauseated and had vomited as he was going upstairs to his room. He noticed some pain in the upper region of the abdomen at the time, and he took a dose of castor oil, which was promptly returned. Not feeling any better, he went to a hospital; an enema was administered, and after about four hours' observation the physician allowed him to return home. He continued to have nausea and abdominal discomfort, so his family physician was consulted; medication was prescribed, apparently for the relief of "ptomaine poisoning," but it was without effect. After an attack of coughing an increase in the severity of his symptoms led him to apply for admission to this hospital.

The chief complaints noted on admission were pain over the upper portion of the abdomen, especially on the right side, nausea, vomiting and "gas on the stomach." The first examiner was impressed principally by the abdominal symptoms and signs, although there was some question in his mind whether the complaints had an organic basis. The abdomen seemed tender over the umbilicus, and the muscles on the right side were slightly rigid. The temperature was 99.2 F.; heart rate, 60; leukocyte count, 9,500. There were a few red blood cells in the urine. The blood pressure was 150 systolic and 90 diastolic. The heart was not enlarged, the rhythm was regular, and no murmurs were heard. It was noted that the peripheral arteries were thickened to a marked degree for so young a man.

During the following month in the hospital the patient did not feel well but did not appear seriously ill. He continued to have inconstant pain in the epigastrium, extending around to the right lumbar region and down the spine, from the intercapsular region to the coccyx. Drinking cold water increased the pain, and after eating he would become nauseated and regurgitate his food. He did not sleep well at night, was constipated and passed only small quantities of urine.

The temperature during this period ranged from 100 to 101 F. On the third day after admission there was leukocytosis (12,000 cells). The erythrocyte count on admission was 4,420,000, and the hemoglobin content was 14 Gm. per hundred cubic centimeters; it dropped to 3,800,000, with a hemoglobin content of 10.5 Gm., in the course of a month. The urine showed a specific gravity of 1.029; no red blood cells were noted after the first specimen. After an intramuscular injection of 1 cc. of phenolsulfonphthalein, he was able to void only one specimen at the end of an hour and none in the ensuing few hours. The specimen voided did not contain enough dye to color the urine when alkalinized. The chemical composition of the blood on the same day was within normal limits.

Studies of the gallbladder showed no abnormalities. Agglutination reactions were negative for typhoid, brucellosis and tularemia. Intestinal tuberculosis was considered, but no acid-fast bacilli were discovered and the gastrointestinal roent-

genograms were normal. The first roentgenogram of the chest (fig. 1) was taken two days after admission; the interpretation was that the heart was slightly enlarged, with widening of the supracardiac shadow. There was a definite projection of the first part of the aorta to the right; the arch was wide, and the

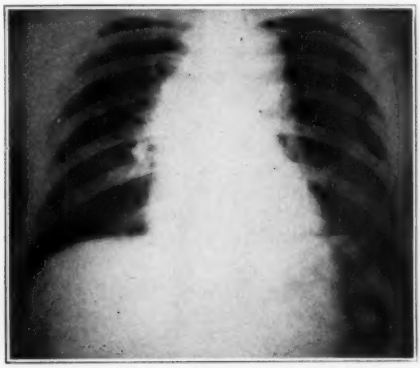

Fig. 1 (case 1).—Roentgenogram taken (at a distance of 6 feet [1.8 meters]) on Dec. 16, 1936, about a week after the onset of symptoms.

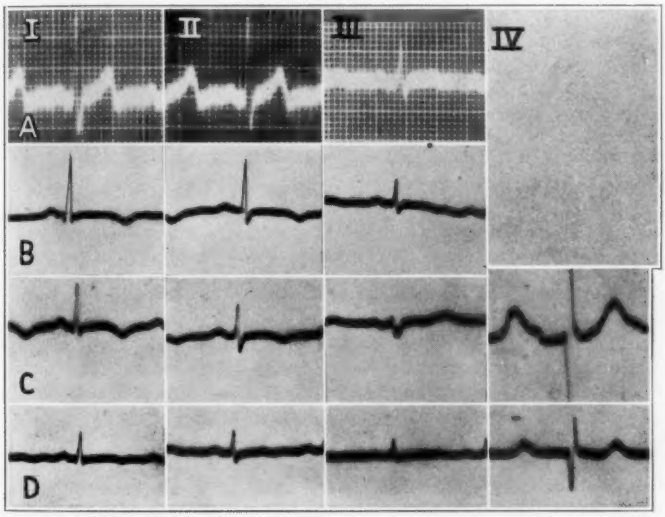

Fig. 2 (case 1).—*A*, taken Jan. 7, 1937, about a month after onset; *B*, Jan. 18; *C*, Feb. 24; *D*, March 2.

knob was broad and rounded. The descending aorta was denser than usual and tended to fill the concavity above the left ventricle. The outline of the aorta appeared ragged, and the trachea was displaced to the right. An electrocardiogram

(fig. 2 *A*) taken about three weeks after admission was essentially normal except for an occasional sinus premature contraction. On several occasions the rhythm of the heart suggested auricular fibrillation, but this was never confirmed by a tracing.

During the second month of his illness the patient felt fairly well although his temperature continued to be slightly elevated. He was able to go home on pass without any untoward effects until, toward the end of the month, the nausea and belching returned and there was pain in the left side of the chest and of the abdomen and in the back. A blood count at the end of the second month showed 3,180,000 red blood cells, with 9.8 Gm. of hemoglobin per hundred cubic centimeters, and 17,950 white blood cells.

A second roentgenogram (fig. 3 *A*) of the heart and aorta was made about this time. The cardiac shadow was greatly enlarged and the supracardiac shadow was wider, although the projection to the right noted in the first film was not observed. Instead, the right border of the aorta formed a wide arc, the more distal and outer portions of which were less dense. The aortic knob was less prominent,

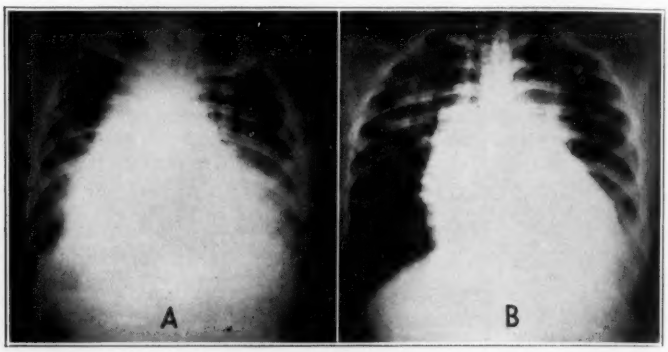

Fig. 3 (case 1).—*A*, roentgenogram taken (at a distance of 6 feet [1.8 meters]) on Feb. 18, 1937. *B*, roentgenogram taken in recumbent position with use of Bucky diaphragm, March 5, 1937.

and the left supraventricular concavity was obliterated. The outline of the borders was still irregular.

Early in the third month of his illness the patient had a sudden attack of pulmonary edema, with marked dyspnea and shock. He did not complain of any particular pain. On examination the heart was appreciably enlarged; there were a gallop rhythm, a transient systolic murmur at the apex and accentuated second sounds at the base.

The patient had several such attacks over a period of forty-eight hours. Between the attacks he was fairly comfortable but occasionally complained of precordial pain. A blood pressure of 166 systolic and 108 diastolic was recorded during this period. The heart sounds did not seem abnormal, and no murmurs were heard.

A third roentgenogram of the heart and aorta (fig. 3 *B*) was taken, using a Bucky diaphragm. The patient was in the recumbent position. This film was not comparable with the previous ones because of the change in position and technic, but it demonstrated the great widening of the aorta, particularly the

descending portion. An electrocardiogram (fig. 2*D*) taken at this time showed inversion of the T waves in leads I and II, with an upright (minus) T wave in lead IV[5] (original technic). The tracing did not suggest the acute changes of a coronary occlusion, although it was interpreted as showing evidence of myocardial damage.

At this time it was noted that arterial pulsation could not be felt in the popliteal, dorsalis pedis or posterior tibial arteries, although the femoral pulses were palpable. On the basis of this absence of pulsation, together with the changes in the roentgenograms of the heart and aorta, the absence of electrocardiographic changes typical of coronary occlusion and the absence of a drop in blood pressure, a diagnosis of dissecting aneurysm of the aorta was made.

The patient continued to have attacks of pulmonary edema, with surprising recovery following each of the acute manifestations. Morphine and atropine, or morphine alone, were always administered and seemed to give relief. It was noticed that the percussion note posteriorly to the left of the spine from the fifth thoracic to the ninth thoracic vertebra was absolutely flat and that a loud, rough systolic murmur could be heard in this region and nowhere else. Also, the patient complained of pain around the left side of the thorax in a segmental distribution.

The patient manifested gradually increasing heart failure and was irrational, screaming out at times. The periodic attacks of dyspnea with pulmonary edema recurred, although the patient appeared comfortable immediately before death, which occurred just three months after admission and ninety-three days after the first symptom. Death was due not to external rupture of the aneurysm but to heart failure.

Postmortem Examination.—The descending aorta presented a transverse tear of the intima across the entire circumference of the vessel, about 10 cm. below the arch. Blood had accumulated within the split coats of the aorta throughout the thoracic and abdominal length of the aorta. About 5 cm. above the bifurcation into the iliac arteries there was a second tear in the intima where a more saccular aneurysm, not connected with the previous one and containing an older, laminated clot, extended along the iliac arteries to Poupart's ligament. There was no evidence of erosion. The wall of the abdominal aorta was blackish and soft.

The pericardial sac contained about 200 cc. of bloody fluid. The hemorrhage apparently originated in an adherent area at the reflection of the pericardium from the aorta. The heart weighed 460 Gm. The muscle was pale but had firm consistency, and on microscopic examination the muscle fibers were seen to be large. The coronary arteries showed only a few patches of atheromatous change.

The left pleural cavity contained several hundred cubic centimeters of serous transudate. The left lung was definitely contracted, due in part to the presence of fluid. The right pleural cavity had synechial adhesions but no clot. Both lungs were quite heavy and solid and were filled with frothy blood-tinged fluid, and in all lobes there were areas of pneumonic consolidation.

Comment.—This patient presented a clinical picture which is less commonly described for dissecting aneurysm of the aorta. The absence of a history of previous hypertension does not necessarily indicate that the blood pressure had not been elevated, although it probably was never

5. The chest electrode was placed over the apex of the heart and connected to the left arm lead. The indifferent electrode was placed on the leg and connected to the left leg lead.

excessively high. There was no history of unusual exertion. Pain was not a prominent symptom; when present it was abdominal, and it did not become thoracic until late in the illness. Nausea and vomiting were the principal complaints; as will be noted in the succeeding histories, these symptoms were common to the other 2 patients from whom a history could be obtained. Low grade fever, leukocytosis, anemia and hematuria, often reported in patients with dissecting aneurysm, were presnet in this case. In retrospect, the rather sharp decline in the number of red cells and in the hemoglobin content during the course of the illness probably indicated loss of circulating blood into the aneurysm; it suggests that such a finding in a patient who survives for more than a few days may be of diagnostic significance.

The progressive changes in the electrocardiograms over the three month period are of some interest. The T waves in leads I to III were upright about three weeks after the onset of symptoms, and the ST segments in leads I and II were slightly elevated. A second tracing taken five weeks later showed inversion of the T waves in leads I and II and without any deviation in the ST interval. Five days later the T waves in leads I and II were again inverted and the T-wave in lead IV was upright (minus). In a tracing about two weeks before death the T waves in leads I and II were less deeply inverted and the T wave in lead III was flat, while the T wave in lead IV continued to be upright (minus). There was a progressive decrease in the voltage of the QRS complexes. These changes were not associated with any gross or microscopic evidence of infarction, and the coronary ostia and arteries were not involved. There was a small amount of fresh blood in the pericardium and a small area of chronic pericarditis with adhesions in the region of the aortic reflection of the pericardium, but it is questionable if the latter was responsible for the changes in the electrocardiogram, which resembled those observed with anterior infarction of the myocardium. Although no structural lesion in the heart was found to account for the abnormalities in the electrocardiogram, the fact remains that they developed after the onset of the dissecting aneurysm.

The roentgenograms also showed progressive changes during the course of the illness and, with the loss of pulsation in the arteries of the lower extremities, made the diagnosis of dissecting aneurysm tenable.

Case 2.—S. M., a white man aged 50, was first admitted to the hospital on Jan. 25, 1937. He stated that except for the usual childhood diseases he had been well until 1911, when he had acute nephritis with uremic coma. He was serving in the Marine Corps at that time and after treatment in the hospital was returned to duty. He was given a medical discharge in 1914, and the subsequent records to 1929 do not show a recorded blood pressure exceeding 130 systolic and 100 diastolic, even during acute attacks of disease.

He had gonorrhea in 1904 but denied any history of syphilis. After discharge from the service he was able to work as a police officer until January 1937, although he had noticed some shortness of breath and slight swelling of his ankles for about six months preceding his admission. Eight years before admission he had had an attack of "stomach trouble," diagnosed as a peptic ulcer and treated as such, with practically complete relief of symptoms.

One day in January 1937 he worked harder than usual, and the next day he had to stay in bed because of knifelike pains in his chest and dyspnea even at rest. The pain was not relieved until he received a hypodermic injection. He seemed to improve for a few days; then his symptoms recurred, with pain, nausea and emesis, extreme dyspnea and palpitation. He became unconscious and was brought to the hospital.

On admission he appeared to be dying, with Cheyne-Stokes breathing, auricular fibrillation (no electrocardiogram was taken) and a blood pressure of 60 systolic

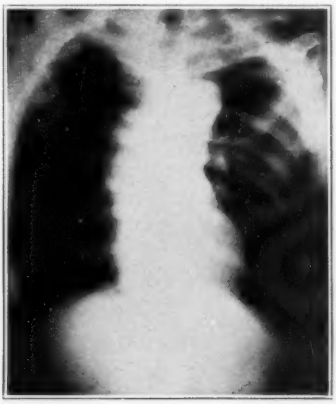

Fig. 4 (case 2).—Roentgenogram taken at bedside on Jan. 27, 1937.

and 40 diastolic. The following morning, however, the pain in his chest was relieved, the blood pressure was 148 systolic and 116 diastolic, and the heart was regular. The borders of the heart could not be satisfactorily determined, and the sounds were distant.

On admission the blood count showed 3,500,000 erythrocytes and 17,250 leukocytes; the hemoglobin was 11.2 Gm. per hundred cubic centimeters. The leukocytosis gradually decreased. Three days after admission the nonprotein nitrogen of the blood was 46.1 mg. per hundred cubic centimeters; the uric acid, 5.4 mg. and the sugar, 78 mg. The urine varied in specific gravity from 1.017 to 1.025. Albumin was found in several specimens; a few white blood cells were always present, and there were red blood cells in 5 of 7 samples. A roentgenogram (fig. 4) taken at the bedside did not reveal any areas of infiltration or consolidation in the lung fields, but the aorta was unusually wide to the right and the aortic knob was prominent and dense, with an irregular shadow extending below to the pulmonary artery. The heart did not appear enlarged.

An electrocardiogram (fig. 5*A*) taken two days after admission revealed a regular sinus rhythm, notched P waves in leads II and III, diphasic T waves in leads I to III and in lead IV a T wave which could not be distinguished from the other undulations in the tracing. Five days later an electrocardiogram (fig. 5*B*) showed definite inversion of all the T waves, deepest in leads II and III. There was no significant change in the ST intervals or in lead IV. These abnormalities were interpreted as evidence of myocardial damage but were not considered characteristic of acute coronary occlusion, although there had been changes in the configuration of the T waves in a period of five days.

The patient improved gradually, except that weakness persisted, and he was allowed to go home after two months of hospitalization, during which period his oral temperature had varied from 97 to 100 F.

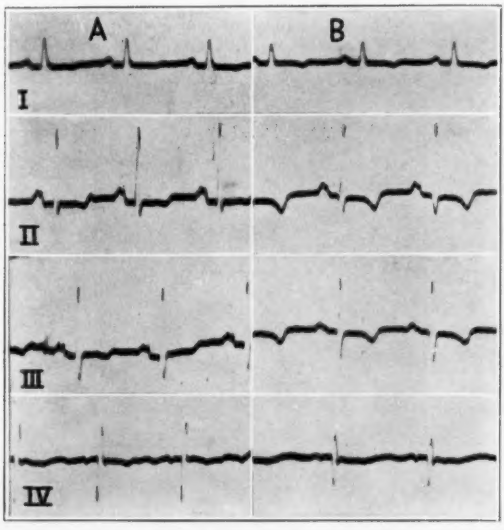

Fig. 5 (case 2).—*A*, taken Jan. 27, 1937; *B*, Feb. 2.

After his discharge from the hospital on March 26, 1937, the patient was more or less invalided because of dyspnea, precordial pain, weakness and palpitation. In late September 1937 he contracted a cold, with severe cough, fever, chills and recurring pains across the front of his chest. The patient was readmitted on Oct. 4, 1937, for treatment of bronchopneumonia; he was obviously very ill, although his oral temperature was only 99.5 F. The breathing was labored but not exceptionally rapid, and he was coughing. The motion of the left side of the chest was markedly reduced, especially over the upper portion. The percussion note to the left above the level of the third interspace was flat, and the breath sounds were practically absent in this area. On the right the percussion note was hyperresonant except posteriorly between the spine and the scapula and anteriorly for 5 or 6 cm. from the sternum, below the second rib. No rales were heard. It was observed that the veins of the left side of the neck and over the midportion of the left side of the chest were dilated.

A roentgenogram (fig. 6*A*) taken at the bedside at this time revealed a large shadow occupying the upper two thirds of the left side of the thorax. There was also a rounded opacity projecting from the cardiac and aortic shadow to the right between the second and fourth ribs anteriorly.

Two days later the patient was improved sufficiently for a roentgenogram to be taken in the erect position with the tube at 6 feet (183 cm.). This plate (fig. 6*B*) presented essentially the same picture as the film taken at the bedside. The "arcuate excrescence" on the right border of the vascular area was more sharply defined, and in both roentgenograms this shadow was more definite and localized than in the plate taken nine months earlier (fig. 5).

The patient's symptoms improved remarkably, and subsequent roentgenograms showed rather sharp demarcation of the shadow in the left upper region of the chest. It seemed most probable that the patient had a tumor of the lung; therefore material for a microscopic study was obtained by use of the bronchoscope, by puncture of the lung and by excision of a lymph node, but none of the specimens showed any abnormality. In spite of the negative results, the patient was given a course

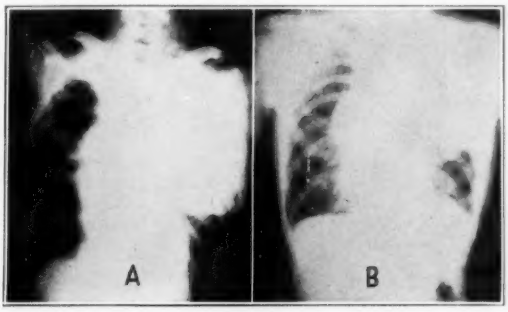

Fig. 6 (case 2).—*A*, roentgenogram taken at bedside Oct. 5, 1937; *B*, taken at a distance of 6 feet, October 7.

of high voltage roentgen therapy to the left lung. A roentgenogram taken about six weeks later (fig. 7*A*) showed some regression of the mass in the left upper region of the chest without change in the opacity to the right of the aorta. Another plate taken six weeks later (fig. 7*B*) showed further decrease in the size of the mass in the left upper region of the chest. The shadow on the right of the aorta was unchanged, and the aortic knob was obviously large and rounded, with a convex shadow filling the concavity between the knob and the left ventricle. This picture suggested a diagnosis of aneurysm, although the shadow in the left lung field was not explained.

The patient continued to improve and except for weakness felt quite well. He was nauseated at times, presumably because of the roentgen treatment, but at other times was able to eat a fair meal. About a week before his death he complained of some difficulty in swallowing liquids. Some edema of the ankles was also noted shortly before death, and, since no rales were heard in the lungs, the edema may have been largely due to his marked anemia rather than to congestive heart failure. In the last week of his life pain in the chest again developed,

and he was noticeably weaker. Death finally ensued after a profuse hemorrhage, in which blood gushed out from the oral cavity.

The laboratory examinations revealed a marked decrease in the number of red cells and in the amount of hemoglobin. There were 1,950,000 erythrocytes and 7 Gm. of hemoglobin, as compared with 3,500,000 erythrocytes and 11.2 Gm. of hemoglobin on the first admission. The urine contained albumin at the time of admission, and there were red blood cells in all of the specimens. The highest specific gravity was 1.022; the excretion of phenolsulfonphthalein was 15 per cent

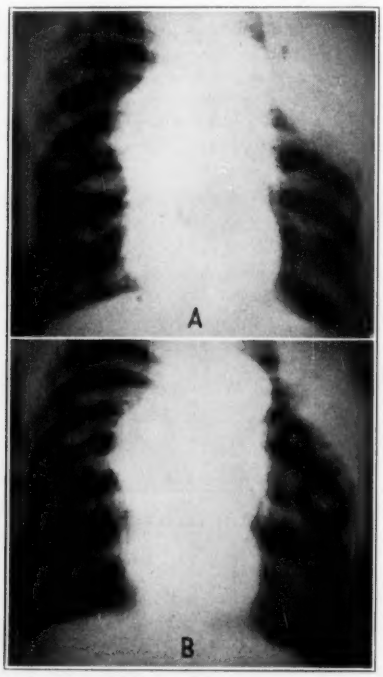

Fig. 7 (case 2).—Roentgenograms taken at a distance of 6 feet; *A*, Dec. 8, 1937; *B*, Jan. 24, 1938.

in two hours. The nonprotein nitrogen was 78.9 mg. per hundred cubic centimeters; the creatine, 2.2 mg.; the uric acid, 8.3 mg.; the sugar 90 mg.

Postmortem Examination.—The body was that of an emaciated white man of about 55 years (actual age, 50). Both pleural spaces contained about 500 cc. of transudative fluid, which was not bloody, and on the upper outer aspect of the left pleura, near the posterior axillary line, there was a globular swelling. When cut into, the mass consisted of soft coagulated material with a yellowish muddy color, which proved to be necrotic blood without organization.

The pericardium contained a slight excess of clear, straw-colored fluid. The heart weighed 340 Gm., which was slightly above the normal limit for a man

who weighed 150 pounds (68 Kg.) in health. The muscle grossly had good consistency, without fibrosis. The coronary arteries were patent and showed a moderate amount of intimal change, with considerable thickening of the wall, especially in the posterior artery. In several areas along the anterior descending artery there were small hemorrhages beneath the intima.

The aorta was inelastic, and the layers of the media were split from the beginning of the aorta to the arch, the fissure extending up into the great vessels of the neck. This space did not contain blood. At the posterior portion of the arch and along the thoracic aorta there appeared to be two sacs within the wall, one extending to the right, in close apposition to the esophagus and filled with a laminated clot, and the other projecting to the left and containing fresher blood. No sign of an intimal tear or of gross communication between the lumen of the aorta and the aneurysm was evident. The esophagus was constricted by the aneurysmal mass, and the mucosal surface in this area presented numerous punched-out ulcers which might have communicated with the aneurysm.

The origin of the blood in the periphery of the lung could not be definitely established, but presumably this blood had issued from a rupture through the adventitia and pleura. All of the bronchi, on both sides, were plugged with blood clots, probably from inspiration of blood during the terminal hemorrhages.

The kidneys were small, red and granular. The capsule of each was adherent, there were several small cysts in the parenchyma, and the cut surface showed a definitely reduced cortex, with white striae running out into it.

There was the scar of a healed ulcer on the anterior wall of the stomach in the prepyloric region.

Comment.—In this case the history was more typical of the classic description of dissecting aneurysm in that the onset was characterized by severe pain following more strenuous exertion than usual. This, however, did not immediately precede the onset of symptoms. Nausea, emesis and, at times, dysphagia were also present. On several occasions there was severe circulatory shock, from which the patient recovered promptly to remain fairly comfortable for considerable periods of time. There were slight fever and leukocytosis at various times during the illness, and the progressive severe anemia was particularly significant. The urine regularly showed red cells, and there was retention of nitrogen in the blood, more marked immediately after acute attacks. The patient gave a history of acute renal disease twenty-six years before, and the renal insufficiency was probably due basically to chronic nephritis plus circulatory impairment subsequent to the development of the aneurysm. The records up to 1929 did not show elevation of the blood pressure, and the absence of marked cardiac hypertrophy would argue against prolonged hypertension.

Two electrocardiograms were taken during the patient's first stay in the hospital, more than a year before his death. In the first one the T waves in the leads I to III were diphasic, while the isoelectric line in lead IV was so irregular that a T wave could not be distinguished. The RS-T intervals were isoelectric. In a tracing taken five days later there was definite inversion of the T waves in leads I to III, with slight

depression of the RS-T intervals in leads II and III. The T wave in lead IV was isoelectric. The patient received only 2 cc. of digifoline-Ciba; this was administered soon after his entrance to the hospital, and none was given subsequently. No electrocardiograms were taken during the second stay in the hospital. The autopsy did not reveal any gross areas of infarction, although a small ecchymotic area beneath the anterior coronary artery showed changes in the muscle indicative of necrosis with replacement by fibrous tissue. This, however, was a year after the electrocardiogram was taken, and the myocardial lesion was probably more recent. There may have been obstruction of the coronary ostia at some time, since the aorta in its first portion was dissected but did not contain blood when examined at autopsy.

The roentgenograms were particularly interesting because of the picture produced by the subpleural hemorrhage and the localized bulgings from the aorta, which led to the clinical diagnosis of pulmonary neoplasm. On the basis of the later roentgenograms, the presence of an aneurysm was suspected, and greater awareness as to the possibility of aortic dissection might have led to the diagnosis early in the course of the second hospitalization.

This patient lived a comparatively long time, perhaps because the aneurysm did not communicate, through an intimal tear, with the lumen of the aorta. This is a relatively uncommon occurrence and may be of importance in the consideration of the pathogenesis.

Case 3.—W. H. D., a white man of 48 years, an office manager, was admitted to this facility on March 18, 1937. The history was obtained from the patient's wife, who stated that he had been well until five years previously, when he began to suffer from faintness, vertigo and severe headaches. At that time his blood pressure was found to be 180 systolic and 120 diastolic. About one year before admission he had dyspnea, orthopnea, cough with blood-streaked sputum, and edema of the ankles; these symptoms had caused him to be bedridden for three months. Recovery from this episode of congestive failure was apparently quite good.

About seven days before admission to the hospital the patient experienced an attack of agonizing pain across the anterior part of the chest and in the back while lifting a heavy object at his home. The pain was severe for more than an hour, and a large dose of morphine was required to give any relief. Associated with the pain were nausea, emesis, dyspnea and cold, clammy sweating. The temperature was 99 F., and two days later, following a chill, it rose to 100 F. He had several attacks of pain of lesser degree after the first one; the following signs and symptoms were observed during one such attack: agonized facies, pallor, cold and perspiring skin; rapid and shallow breathing; clutching at the right posterior side of the chest with the left hand. The blood pressure was maintained in the region of 160 systolic and 120 diastolic, although it had been as high as 220 systolic and 150 diastolic before admission to the hospital. Death occurred on March 20, 1937, nine days after the onset of symptoms.

On admission the erythrocyte count was 3,750,000; the hemoglobin content, 13.5 Gm.; the leukocyte count, 17,500. The urine was normal. An electrocardiogram

was not obtained. A roentgenogram (fig. 8) taken at the bedside showed a wide supracardiac shadow, widening of the left border of the heart and an opacity in the right pulmonary field.

Postmortem Examination.—The aorta was dilated but retained considerable elasticity, and the intimal surface was quite smooth up to the origin of the great vessels from the arch. Just beyond the opening of the left subclavian artery there was an irregular tear in the intima, extending somewhat transversely for about 4 cm. The layers of the aorta were dissected in both directions from this area for some distance, and there was a rupture through the external coats opposite the intimal tear. This opened into the posterior mediastinum, which contained large clots on both the left and the right side, with extension into the neck.

The heart weighed 600 Gm. The pericardium contained about 20 cc. of serosanguinous fluid, and beneath the visceral pericardium, especially over the left

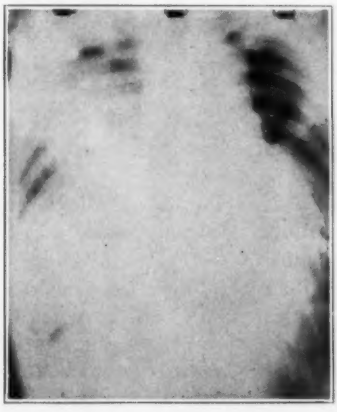

Fig. 8 (case 3).—Roentgenogram taken at bedside March 18, 1937.

auricular appendage, there was a hemorrhagic infiltration. The coronary arteries were not particularly sclerotic.

Both pleural cavities contained about 250 cc. of serosanguinous fluid. The lungs were partially collapsed, dry and pale.

Comment.—The history in this case fits the "classic" description of dissecting aneurysm. The patient was known to have had hypertension for several years, and a sudden attack of agonizing pain developed during strenuous exertion. The blood pressure tended to be maintained at a moderately high level except during shock associated with pain. The dissection was relatively limited. There were no consolidated or congested areas in the lungs to explain the shadow observed in the right lung field on the roentgenogram; this must have been associated with the contiguous hemorrhage into the mediastinum.

Case 4.—B. A., a white man of 39 years, was admitted to this facility on Sept. 7, 1937, and died shortly after admission. Practically no history is available except

that he had complained of severe substernal pain before coming to the hospital, although his principal complaint when he was seen in the hospital was pain in the left leg.

Postmortem Examination.—The pericardium contained about 1,000 cc. of blood, part of it clotted. The heart weighed 585 Gm., and the muscle had firm consistency.

The ascending aorta was dark colored because of the blood in the wall, which considerably reduced the lumen of the vessel. There was a tear through the intima, about 2 cm. in length, just above the sinuses of Valsalva; it communicated with the pericardial sac through a small opening proximal to the pericardial reflection on the aorta. There was a longer tear in the intima, distal to the first, extending longitudinally almost to the arch of the aorta. The outer coats of the ascending portion of the aorta were dissected. The wall of the descending and abdominal portions appeared intact, but at the bifurcation of the common iliac artery there was a small amount of clot in the wall without any intimal rupture.

Comment.—Rupture into the pericardium is a fairly common terminal event in dissecting aneurysm.

COMMENT

Since the clinical manifestations of dissecting aneurysm have been so adequately reviewed in recent publications,[6] only a few of the features of this condition will be emphasized.

A common description [6d] of the onset of symptoms in dissecting aneurysm is that the patient "suddenly experiences an agonizing, tearing pain, usually in the anterior portion of the chest . . . which feels as though something has been torn loose inside." Pain, indeed, is usually an outstanding symptom of dissecting aneurysm, and this diagnosis should be considered when pain is referred to the anterior part of the chest. It must be noted, however, that cases have been reported in which there was no complaint [7] of pain referred to the chest. In some of these cases the patient was conscious of oppression or constriction in

6. (*a*) Blackford, L. M., and Smith, C.: Coronary Thrombosis vs. Dissecting Aneurysm in Differential Diagnosis, J. A. M. A. **109**:262 (July 24) 1937. (*b*) Claiborne, T. S., and Holler, E. D.: Dissecting Aneurysm of the Aorta, Am. Heart J. **15**:358, 1938. (*c*) Boyd, L. J., and Werblow, S. C.: Coarctation of the Aorta, Dissecting Aneurysm and Aneurysmal Dilatation of the left Vertebral Artery, Ann. Int. Med. **11**:845, 1937. (*d*) McGeachy, T. E., and Paullin, J. E.: Dissecting Aneurysm of Aorta, J. A. M. A. **108**:1690 (May 15) 1937. (e) Peery, T. M.: Dissecting Aneurysm of the Aorta, Am. Heart J. **12**:650, 1936. (*f*) Osgood, E. F.; Gourley, M. F., and Baker, R.: Diagnosis of Dissecting Aneurysm of the Aorta, Ann. Int. Med. **9**:1398, 1936. (*g*) Roesler, H.; Gifford, U. G., and Betts, W.: Dissecting Aneurysm of Aorta, Am. Heart J. **13**:426, 1937. (*h*) Wood, F. C.; Pendergrass, E. P., and Ostrum, H. W.: Dissecting Aneurysm of the Aorta, Am. J. Roentgenol. **28**:437, 1932. (*i*) White, P. D.; Badger, T. L., and Castleman, B.: Dissecting Aortic Aneurysm Wrongly Diagnosed Coronary Thrombosis, J. A. M. A. **103**:1135 (Oct. 13) 1934. (*j*) Shennan.[2] (*k*) Hamburger and Ferris.[3] (*l*) Glendy and others.[4a] (*m*) Weiss.[4b]

7. Wood and others.[6h] Hamburger and Ferris.[3]

the chest. As in coronary occlusion, the patient often does not remember or is incompetent to give details of his history, and the failure to elicit a definite history of pain does not necessarily preclude a diagnosis of dissecting aneurysm. One of our patients, who was semicomatose when admitted to the hospital, complained only of pain in his leg, although other informants stated that earlier he had located the pain in his chest.

Two other patients had pain in the chest at the onset, but in only 1 (case 3) did this symptom resemble that of the "classic" description; in the fourth patient (case 1) the pain was always referred to the abdomen until shortly before death. In this patient the descending and abdominal portions of the aorta were principally involved. Abdominal pain is quite common; it was the principal complaint in 30 of Shennan's 300 cases and in 15 of 50 recently reported. Pain may also be referred to the back, shoulders and other locations; in fact, the pain of dissecting aneurysm does not follow any definite pattern or have any particular location, and one is impressed by its tendency to migrate to different anatomic regions. Glendy, Castleman and White [48] pointed out that the radiation of the pain was rarely the same in any 2 of their patients.

In addition to these characteristics, a suggestive diagnostic feature is a sudden and dramatic onset of catastrophic symptoms, which may be surprisingly relieved, even without medication, if the patient survives the original attack. Symptoms tend to recur after intervals of relative comfort varying from hours to months, although in some cases the pain never recurs and the patient lives to die of some other cause.

The occurrence of fever, of gastrointestinal symptoms such as vomiting and dysphagia, of severe circulatory collapse with low blood pressure from which the patient may recover remarkably and of nervous symptoms such as paralysis and unconsciousness has already been noted. The laboratory examinations in our cases revealed leukocytosis and anemia; the latter was particularly significant in that it progressed during the course of the illness, presumably because of loss of circulating blood into the aneurysm and other tissues. In relation to such anemia, Osgood, Gourley and Baker [67] observed an increased icterus index, which they ascribed to destruction of hemoglobin. There was also evidence of renal insufficiency in 2 of our patients, manifested by azotemia in 1 and by albuminuria, hematuria and low dye excretion in both. In addition, 1 patient voided only small amounts of urine. The patient with azotemia had had renal disease, but his nitrogen retention greatly decreased following recovery from the acute phase of the dissecting aneurysm. It is probable that the renal blood flow was impaired in both cases by the reduction in the lumens of the tributaries at their orifices.

When pain in the chest is a presenting symptom, electrocardiographic evidence is often of great value in differentiating the possible causes. The data are not sufficient to establish what changes in the electrocardiogram, if any, are associated with dissecting aneurysm. In only 15 of 127 cases collected [6d] from the English literature up to 1937 were electrocardiograms reported. In some instances there were no deviations from the normal. White, Badger and Castleman [6i] took three tracings within four days on a patient with dissecting aneurysm which did not vary in any essential detail and did not show any abnormality. Claiborne and Holler [6b] reported four tracings on a patient which showed only gradually decreasing voltage of the QRS complexes. The T wave in lead III was inverted in all tracings.

Others have reported electrocardiograms in cases of dissecting aneurysm which resemble those in cases of myocardial damage due to coronary occlusion. Glendy, Castleman and White [4a] showed a tracing with slight changes in the T waves in leads II and III suggestive of posterior occlusion. The right coronary ostium was involved in the aortic dissection.

McGeachy and Paullin [6d] described a series of six electrocardiograms on a patient with dissecting aneurysm in which T in lead I varied from upright to inverted, then became upright again and finally inverted. T in lead II showed increasing voltage as an upright wave and subsequently became diphasic. T in lead III was upright in all tracings, and in some it was of high voltage. In all of the electrocardiograms there was a tendency for the ST segment to be depressed in leads I and II and to be slightly elevated in lead III. The QRS complex in lead III tended to be monophasic downward, or diphasic with a deep Q wave. The changes observed in this series of electrocardiograms might be interpreted as evidence of acute myocardial damage which could not be localized to any particular aspect of the heart. Since the pericardium contained a large quantity of clotted blood, myocardial damage may have been responsible for the changes, although there was no mention of myocardial abnormalities other than hypertrophy.

Osgood, Gourley and Baker [6f] described two tracings from a patient with dissecting aneurysm, taken three and one-half months apart. In the first, the T waves in leads I and II were inverted, with slight depression of the ST segments in both leads. In the second tracing the depression of the ST segments in leads I and II was marked, with elevation of the ST segment in lead III. No infarction of the myocardium was found at autopsy. The ST segment in an electrocardiogram taken on a second patient with dissecting aneurysm also showed depression of the ST segment in leads I and II and elevation in lead III.

Hamburger and Ferris [8] described three electrocardiograms taken on a patient in which the T waves in leads II and III gradually became

inverted, with development of a deep Q wave in lead III. The ST segment became definitely elevated in leads II and III and slightly elevated in lead I, while the T wave in lead IV reversed its direction, apparently, from positive to negative. Except for the T wave in lead IV and the ST segment in lead I this would usually be considered evidence of damage to the posterior wall secondary to occlusion of the posterior artery. There was subepicardial hemorrhage surrounding the posterior artery about 1 cm. below its origin, although it was not stated whether the lumen was decreased. There was no evidence of a myocardial infarct, and the authors did not think the pericardial hemorrhage was responsible for the electrocardiographic changes, since it must have been a terminal event.

The electrocardiographic abnormalities noted in my cases and in those reported by others indicate that the absence of changes in the electrocardiogram should help to eliminate coronary occlusion in the differential diagnosis of dissecting aneurysm, while the converse is not true. After the onset of dissecting aneurysm abnormalities may appear in the electrocardiogram which have no characteristic pattern but often may simulate that of acute coronary occlusion. Furthermore, there may be progressive changes in the various complexes, as in coronary occlusion, which do not indicate any particular pattern of localization. It is therefore not possible to exclude the diagnosis of dissecting aneurysm on the basis of noncharacteristic electrocardiographic abnormalities.

Roentgenography should offer considerable aid in the diagnosis of dissecting aneurysm, but unfortunately many patients are too ill to permit a satisfactory examination, and it is questionable whether a patient should be subjected to the exertion of having a teleroentgenogram taken when a dissecting aneurysm is suspected. Occasionally, as in 2 of our cases, the condition of the patient is not so grave, and the additional information to be derived warrants taking roentgenograms. Wood, Pendergrass and Ostrum [6h] described the roentgenologic features in 7 cases. They directed attention to the deformity of the supracardiac shadow, which may be a mere widening or may be an arcuate excrescence arising from some part of the aorta. They think that an extension of the shadow along a cervical vessel is the most pathognomonic roentgenologic feature, although it is infrequently seen. Roesler, Gifford and Betts [6g] pointed out that if an "aneurysm involves only a part of the circumference of the aortic vessel and has a predominantly lateral location with respect to the direction of projection, it will be visualized as an outer, lighter shadow." When possible, therefore, it is desirable to obtain oblique and lateral as well as sagittal projections. Since the majority of dissections occur in the ascending aorta, deformity of the shadow of this portion should be most common. It may be difficult to

differentiate the changes that occur in hypertension, aortitis or even mediastinal tumor from those of dissecting aneurysm, but displacement to the right of either the trachea (as in case 1) or the barium-filled esophagus offers suggestive evidence of gross enlargement of the arch. Irregularity in the outline of the shadow is often conspicuous and is also suggestive.

Since the dissection, if not immediately fatal, tends to be progressive, serial roentgenograms may clearly show changes which can be accounted for best by hemorrhage into the structure involved. In case 1 the changes in the roentgenogram led to the antemortem diagnosis, while in case 2 the interval between the examinations was so long that a rapidly growing neoplasm might have produced the abnormalities observed. The differentiation was further complicated in this instance by the large opacity in the left upper part of the chest. Fluid has been noted frequently in the left pleural cavity and occasionally in the right, but it is usually seen at the base of the cavity. In one of the cases reported by Wood, Pendergrass and Ostrum [6h] there was an extension of the shadow of the aortic knob which partially obscured the left upper portion of the chest, and they mention that in 2 of their cases nonfatal rupture of the aneurysm into the mediastinum occurred. It is necessary, therefore, to consider the possibility of hemorrhage into the lung, pleura and mediastinum from a dissecting aneurysm in the differentiation of shadows in the lung fields, especially when there is deformity of the supracardiac shadow.

The causes of dissecting aneurysm deserve some comment. The conception that the dissection is always or even usually dependent on a primary rupture of the intima followed by escape of blood from the lumen into the wall of the vessel is not acceptable. One of our patients presented a massive dissection of the aorta without any apparent break in the intima, and the fourth showed a small isolated hemorrhage with dissection without intimal rupture. Intimal tears were not observed in 2 of the cases observed by Hamburger and Ferris,[8] and Winternitz [8] made the statement that "there can be no doubt that the dissecting aneurysm arises from hemorrhage within the vessel wall; it does not have its origin from a tear of the innermost surface." Indeed, intimal tears and acute rupture of all coats may occur without dissection. Shennan questioned whether the pressure in the vasa vasorum is high enough to act as a dissecting force, in commenting on the dissecting aortitis described by Babes and Mironescu, and assumed that "the local splitting is favored by degenerative changes in the media, which must accompany and are really dependent on the vascular alterations." Peery,[6e]

8. Winternitz, M. C.; Thomas, R. M., and LeCompte, P. M.: Studies in the Pathology of Vascular Disease, Am. Heart J. **14**:480, 1937.

Shennan[2] and others have described degenerative and inflammatory changes in the media of the aorta. Those which Shennan observed were seldom localized, but usually widespread; he concluded that degeneration of the media, due to toxins in most cases, was "the most important determining factor in the causation of dissecting aneurysm." Peery stated that it was a general belief that disease of the aortic wall, usually of an atherosclerotic nature, was the most important factor predisposing to dissection. Since dissection occurs in arteries with comparatively little intimal change—without intimal rupture and usually with no changes closely related anatomically to those of atheroma—it seems more probable that the primary disease involves the inner coats rather than the intima. Whether this damage is due to toxins or to vascular changes cannot be definitely established at present. Certainly hemorrhage into the walls of blood vessels from the vasa vasorum is not uncommon and may be extensive enough to fill an aneurysm of considerable size. Both the intimal rupture usually observed and the external rupture may be comparatively late events.

SUMMARY

Four cases of dissecting aneurysm, with postmortem examinations, are reported. In 1 case the diagnosis was made before death.

Two cases were observed for periods of three months and fourteen months respectively. The changes present in the electrocardiograms and roentgenograms in these cases are discussed.

The absence of the typical pain of the syndrome was conspicuous in 3 cases, although in all cases severe symptoms developed rather abruptly.

There was severe progressive anemia in 2 cases.

The absence of intimal rupture in 1 case suggests that intramural changes may be important in the causation of dissecting aneurysms.

HYPERTHYROIDISM AND DIABETES

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In 1926 one of us (Wilder[1]) reported a study of 38 cases of hyperthyroidism and diabetes. The patients were observed during the period from Jan. 1, 1923, to Dec. 31, 1925, inclusive. The present study is that of a series of patients seen during a similar period, from Jan. 1, 1935, to Dec. 31, 1937, inclusive. The patients in both series were divided into two groups—those with exophthalmic goiter, and those with adenomatous goiter and hyperthyroidism, according to Plummer's classification.[2] In order to exclude any but true diabetic patients we used Joslin's standard for diagnosis of diabetes in hyperthyroidism, which, as stated in his book, is a blood sugar content of 0.15 per cent during fasting or of 0.20 per cent or more after meals, in addition to glycosuria.

Table 1 shows the frequency of occurrence of diabetes combined with hyperthyroidism. A comparison is made with the figures obtained in 1926. Data for the frequency of occurrence of diabetes with adenomatous goiter without hyperthyroidism have been included in the later series.

During the interval of twelve years between reports the incidence of frank diabetes as a complication of hyperthyroidism has increased from 1.1 per cent to 3.2 per cent. As in the first report, its occurrence is more frequent in adenomatous goiter with hyperthyroidism (5.6 per cent) than in exophthalmic goiter (1.7 per cent). The fact that exophthalmic goiter occurs in a younger age group may partially explain this discrepancy. The average age of the patients with exophthalmic goiter and diabetes was 50.3 years, and that of patients with adenomatous goiter with hyperthyroidism and diabetes was 56.6 years. Another explanation

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Read at the meeting of the American Association for Study of Goiter, Rochester, Minn., April 17, 1940.

1. Wilder, R. M.: Hyperthyroidism, Myxedema and Diabetes, Arch. Int. Med. **38**:736-760 (Dec.) 1926.

2. Boothby, W. M., and Plummer, W. A.: Diseases of the Thyroid Gland, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1936, vol. 3, pt. 2, pp. 839-964 (43).

is to be found in the duration of the hyperthyroidism in the two groups. Patients with exophthalmic goiter seek medical attention earlier, as a rule, than do those with the more insidious form of hyperthyroidism accompanying adenomatous goiter. Therefore, more opportunity for precipitating diabetes is given by adenomatous goiter with hyperthyroidism.

An attempt was made to ascertain the priority in appearance of symptoms of diabetes or hyperthyroidism. Owing to the uncertain onset of each disease and to the fact that certain symptoms, notably bulimia, loss of weight and weakness, are common to the two conditions, satisfactory conclusions frequently could not be reached. That the hyperthyroidism preceded in many cases is, however, quite clear.

TABLE 1.—*Incidence of Combined Diabetes and Hyperthyroidism* *
(Jan. 1, 1935 to Dec. 31, 1937, Inclusive)

Disease	Cases		Complicating Disease	1923-25		1935-37	
	1923-25	1935-37		Cases	Per Cent of Total	Cases	Per Cent of Total
Adenomatous goiter with hyperthyroidism	1,131	750	Diabetes	23	2.0	42	5.6
Exophthalmic goiter	2,340	1,132	Diabetes	15	0.6	19	1.7
Adenomatous goiter with hyperthyroidism plus exophthalmic goiter—total	3,471	1,882	Diabetes	38	1.1	61	3.2
Adenomatous goiter without hyperthyroidism	.....	2,277	Diabetes	..	...	38	1.67

* In these counts, patients entering because of recurrence of hyperthyroidism within the three year period are counted more than once. The number of these, however, is too small to affect the significance of this table.

In the series of 1,132 patients with exophthalmic goiter seen at the clinic from 1935 to 1937, inclusive, there were 19 who had diabetes. Eleven were women, and 8 were men. Six did not require insulin for control of diabetes. The others required from 15 to 180 units per day; the average was 50 units per day. The basal metabolic rate varied from + 9 to + 97 per cent; the average was + 38 per cent. Thirteen patients were operated on. Within the first few weeks after operation their basal metabolic rates varied from — 14 to + 34 per cent (average + 8 per cent). The insulin requirement of 5 patients increased immediately after operation but, with that of the rest of the patients on whom operation was performed, it fell below or to the preoperative maintenance level within fourteen days. Ten of the patients who were operated on required much less insulin than they had taken on admission to the clinic. In 2 patients acidosis developed immediately after operation, but this was easily controlled. Seven of the 19 patients in this group had recurrent exophthalmic goiters. One patient died in

coma two days after dismissal from the clinic; thyroidectomy had been advised but was refused.

In the series of 750 patients who had adenomatous goiter with hyperthyroidism, 42 also had diabetes. The female sex predominated, as in the previous group, but to a much greater degree—34 of 42 as compared with 11 of 19.

The basal metabolic rate of the 42 patients studied in this group ranged from + 3 to + 57 per cent; the average was + 27 per cent. Twenty-nine of these patients were operated on. Within the first few weeks after operation their basal metabolic rates varied from — 8 to + 26, average + 10 per cent. The doses of insulin given preoperatively ranged from 10 to 140 units per day. The average dose was 50 units per day. The insulin requirements of 12 patients increased during the first few postoperative days. In all but 5 of the patients who were operated on the requirement fell below the preoperative maintenance level within two weeks. In 4 patients acidosis developed postoperatively. This was readily controlled. One patient died on the sixth postoperative day. Death in this instance was due to cerebral arteriosclerosis and infarct of the brain.

Fitz,[3] in 1921, stated that nontoxic thyroid disease does not affect diabetes. In his series the patients with nontoxic goiter who were operated on showed no improvement of the diabetes. Wilder in 1926 came to the same conclusion. In the present series there were 38 patients with adenomatous goiter and diabetes but no clinically evident hyperthyroidism. Their average age was 57.4 years. Women predominated as in the other groups, the ratio being 22 to 16. The basal metabolic rates ranged from — 16 to + 14 per cent; the average was + 2 per cent. Sixteen patients required insulin for control of the diabetes. The remainder were treated with dietary restrictions. The doses of insulin ranged from 15 to 115 units per day, the average being 42 units. Thyroidectomy was performed on 7 of these patients. Their basal metabolic rates preoperatively ranged from + 1 to + 13 per cent; the average was + 8 per cent. Four required insulin preoperatively in doses of 11 to 50 units daily. Six required insulin for several days postoperatively in doses of 15 to 120 units daily. One patient who had not taken insulin before operation required 70 units on the fourth postoperative day. Later her diabetes was readily controlled without insulin.

The following case report is an example of severe exacerbation of diabetes that at times may be observed postoperatively in patients with adenomatous goiters associated with normal basal metabolic rates and

3. Fitz, R.: The Relation of Hyperthyroidism to Diabetes Mellitus, Arch. Int. Med. **27**:305-314 (March) 1921.

no clinical evidence of hyperthyroidism. The observation is believed to have important clinical significance and heretofore has received no comment in the literature.

REPORT OF A CASE

A man 54 years of age presented himself for examination with no other complaint than fatigue of about two years' duration. Polyuria and polydipsia had been noted for several weeks, but the urine had not been examined for sugar. The maximal body weight of 250 pounds (113.4 Kg.) had been reached eleven years previously, and, partly by dieting, had been reduced to 205 pounds (93 Kg.). In the last year an additional 9 pounds (4.1 Kg.) had been lost.

Examination showed a man weighing 196 pounds (88.9 Kg.) with a blood pressure of 154 systolic and 100 diastolic and a pulse rate of 96 per minute. The thyroid was enlarged and was very hard. The condition of the thyroid had been noted in a previous examination at the clinic in 1927, but operation had not then been advised. Examination of the urine revealed the presence of a trace of reducing substance, and a determination of the blood sugar during fasting revealed 226 mg. per hundred cubic centimeters. The basal metabolic rate was +4 (two tests). The clinical diagnosis was adenomatous goiter without hyperthyroidism.

A diet containing 238 Gm. of carbohydrate was prescribed. Also, compound solution of iodine was given. It was found necessary to use 25 units of insulin daily to control glycosuria. After ten days, the fasting blood sugar being 161 mg. per hundred cubic centimeters, operation was performed. Intense glycosuria followed and for the next seven days was controlled with difficulty. The daily doses of insulin were 95, 115, 60, 70, 55, 55 and 80 units, and the amounts of sugar in the urine for the first four of these days were 17, 29, 12 and 30 Gm. respectively. All specimens also contained acetone and diacetic acid. Otherwise, the degree of postoperative reaction seemed not abnormal. The maximal temperature reached, on the third day, was 102 F., and after the fourth day the patient was free from fever. Subsequently the doses of insulin could be rapidly decreased, so that by the end of the second week 12 units of protamine zinc insulin in one dose daily was sufficient to prevent glycosuria. Although the postoperative behavior of this patient was cause for some apprehension, the ultimate result was entirely satisfactory. The report of the pathologist on the tissue removed at operation was as follows: weight 160 Gm.; multiple, hyaline, hemorrhagic, cystic fibrous, calcareous, degenerating, fetal and colloid adenomas in a colloid thyroid.

FOLLOW-UP OF CASES IN 1926 STUDY

A complete follow-up study was made of all the 38 cases of hyperthyroidism with diabetes reported by one of us (Wilder) in 1926. In 12 of the 15 cases of exophthalmic goiter and diabetes operations were done. In 7 of these the patients have survived thyroidectomy an average of thirteen and eight-tenths years. The average duration of life in the five cases in which death has occurred was eight and one-tenth years after thyroidectomy. Death in these cases was attributed to coma, diabetes, lobar pneumonia, coronary thrombosis and heat stroke. Two of the 3 patients who were not operated on died of coma, and the other died with diabetes within a few months after dismissal.

Twenty-one of the 23 patients with adenomatous goiter with hyperthyroidism and diabetes were operated on. Five of these now are living, having survived thyroidectomy an average of thirteen and six-tenths years. The average duration of life in the 16 cases in which death has occurred was seven and four-tenths years after thyroidectomy. The causes of death were: heart disease, 7; pneumonia, 3 and coma, gangrene (right leg), carbuncle on the back of the neck, cerebral hemorrhage, recurrent carcinoma and acute cholecystitis, 1 each. One of the 2 patients not operated on died of cardiac decompensation three months after admission. The other died ten years later of cardiac and renal disease.

Joslin has reported the average duration of life, subsequent to the onset of diabetes, among deceased ex-patients of all ages in the early Banting (1922-1926), middle Banting (1926-1930) and later Banting (1930-1935) periods as seven and six-tenths, eight and four-tenths and eleven years respectively. When all the patients in Wilder's series of 1926 are considered, except the 5 who did not have thyroidectomy, the average duration of life subsequent to the onset of diabetes was twelve and four-tenths years. When only those patients who now are dead are considered, again excluding the 5 who did not have thyroidectomy, the average duration of life subsequent to the onset of diabetes was ten and eight-tenths years. The numbers in both of these groups are too small to justify comparison with the large groups (514, 897 and 981 cases respectively) of Joslin's deceased patients with diabetes studied by the statistical bureau of the Metropolitan Life Insurance Company. They, nevertheless, support the assumption that patients with hyperthyroidism and diabetes who receive satisfactory surgical treatment for their hyperthyroidism do as well as patients with diabetes free of this complication. The fact that 4 of the 5 who were not operated on died within a few months of the time they were dismissed from the clinic emphasizes the importance of performing thyroidectomy in cases of associated hyperthyroidism and diabetes.

COMMENT

Thyroxine has been shown to increase both anabolic and catabolic processes within the cells, the effects depending on the amount used. The metabolism of fats, carbohydrates and proteins is affected, and the distribution of minerals and water is also modified. Kendall [4] stated:

> These observations suggest that the changes which are associated with a marked increase in the B. M. R. are but an exaggeration of the normal metabolic activity of the cell without distortion and with utilization of metabolites according to their

4. Kendall, E. C.: The Influence of Some of the Ductless Glands on Metabolic Processes, Endocrinology **24**:798-805 (June) 1939.

availabilities. The only change is in the capacity for production of energy. However, when another hormone, as insulin or cortin, is deficient then the symptoms caused by the deficiency are aggravated and the fault in the metabolic processes becomes more marked when thyroxine is administered even in relatively small amounts.

The clinical observations recounted fully confirm this opinion. With the onset of hyperthyroidism previously existent diabetes is intensified, and with correction of the hyperthyroid state by thyroidectomy the intensity of the accompanying diabetes is diminished.

Further study reveals that the decreased incidence of hyperthyroidism among diabetic patients was coincident with the decline in the number of all hyperthyroid patients coming to the clinic.

The incidence of diabetes in patients with exophthalmic goiter for the period 1935 to 1937, inclusive, was 1.7 per cent. This is the same as the incidence of diabetes among all new patients registering at the clinic during the same period. With regard to the incidence of diabetes in patients with adenomatous goiter and hyperthyroidism there is a different story. During the same period 5.6 per cent of all patients with adenomatous goiter and hyperthyroidism had diabetes. This percentage was over three times that for the incidence of diabetes among new patients registering at the clinic. As shown in table 1, Wilder reported an incidence of 2.0 per cent in 1926, which at that time was nearly twice the incidence of diabetes among new patients. Joslin and Lahey [5] reported 28 instances of diabetes among 655 patients with secondary hyperthyroidism, an incidence of 4.3 per cent. That age is not the factor explaining this high incidence of diabetes in the patients with adenomatous goiter and hyperthyroidism (whose average age was 56.6 years) is shown by the occurrence of diabetes in only 1.67 per cent of the patients with adenomatous goiter without hyperthyroidism (whose average age was 57.4 years).

The incidence of diabetes among patients with adenomatous goiter without hyperthyroidism was, as just stated, 1.67 per cent. This was about the same as among new patients registering at the clinic, 1.7 per cent. Surgeons must handle such patients with the same care that is indicated when the goiter is toxic. Occasionally there is marked increase in the severity of the diabetes, usually beginning within the first twenty-four hours after thyroidectomy, and lasting two to five days. The most logical explanation of the phenomenon is the mechanical liberation of large amounts of thyroid hormone as a result of operation, the absorption of the hormone leading to a temporary increase in the rate of metabolism and an accompanying requirement for more insulin.

5. Joslin, E. P., and Lahey, F. H.: Diabetes and Hyperthyroidism, Am. J. M. Sc. **176**:1-22 (July) 1928.

Thyroidectomy was performed on 42 of the 61 patients with hyperthyroidism and diabetes. There was 1 fatality, which occurred in the case of a woman aged 73 who died on the sixth postoperative day. As stated before, postmortem examination revealed cerebral arteriosclerosis and infarct of the brain.

SUMMARY

Sixty-one cases of frank diabetes combined with states of hyperthyroidism were studied. Diabetes occurred with a frequency of 3.2 per cent in all cases of hyperthyroidism. The incidence in cases of exophthalmic goiter was 1.7 per cent; in those of adenomatous goiter with hyperthyroidism it was 5.6 per cent. In the latter group the evidence clearly indicates that hyperthyroidism was a factor of etiologic significance in the precipitation of the diabetes.

Thirty-eight patients with diabetes and adenomatous goiter without clinical evidence of hyperthyroidism were studied. Thyroidectomy was performed on 7 of these patients. Six required large postoperative doses of insulin, and difficulty was encountered in the control of their diabetes for the first three to five postoperative days. The case of 1 such patient is reported in detail.

A follow-up study was made of Wilder's 38 patients who had hyperthyroidism with diabetes. When those who did not have thyroidectomy were excluded, the average duration of life after the onset of diabetes was found to be 12.4 years. The data obtained support the assumption that patients with hyperthyroidism and diabetes who receive satisfactory surgical treatment for their hyperthyroidism do as well as patients with diabetes free of this complication, whereas those who are not relieved by operation fare badly.

CLINICAL MANIFESTATIONS OF PAROXYSMAL HYPERTENSION ASSOCIATED WITH PHEOCHROMOCYTOMA OF ADRENAL

REPORT OF A PROVED AND OF A DOUBTFUL CASE

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Paroxysmal hypertension due to an adrenal medullary tumor may progress so far as to cause death from irreparable vascular damage, or death may ensue from other causes. The disease can be diagnosed in its early stages and eradicated by surgical intervention. There are excellent reviews of the literature by Belt and Powell,[1] Wells and Boman,[2] Nuzum and Walton,[3] Edward,[4] Lazarus and Eisenberg [5] and Coller, Field and Durant.[6] Although there have been many valuable case reports, including those of the authors just mentioned as well as those of Beer, King and Prinzmetal,[7] Evans,[8] Holst,[9] Binger and Craig,[10]

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1. Belt, A. E., and Powell, T. O.: Chromaffin Cell Tumors of Suprarenal Medulla: Clinical Manifestations of the Chromaffin Cell Tumors Arising from the Suprarenal Medulla, Surg., Gynec. & Obst. **59**:9-24 (July) 1934.

2. Wells, A. H., and Boman, P. G.: The Clinical and Pathologic Identity of Pheochromocytoma, J. A. M. A. **109**:1176-1180 (Oct. 9) 1937.

3. Nuzum, F. R., and Walton, J. W.: Paroxysmal and Persistent Hypertention in Association with Lesions of the Adrenal Glands, Am. Heart J. **16**:643-662 (Dec.) 1938.

4. Edward, D. G.: Pheochromocytomata and Hypertension, J. Path. & Bact. **45**:391-403 (Sept.) 1937.

5. Lazarus, J. A., and Eisenberg, A. A.: Tumors of Adrenal Gland: Report of Two Cases of Paraganglioma of Adrenal Gland, J. Urol. **27**:1-26 (Jan.) 1932.

6. Coller, F. A.; Field, H., Jr., and Durant, T. M.: Chromaffin Cell Tumor Causing Paroxysmal Hypertension Relieved by Operation, Arch. Surg. **28**:1136-1148 (June) 1934.

7. Beer, E.; King, F. H., and Prinzmetal, M.: Pheochromocytoma with Demonstration of Pressor (Adrenalin) Substance in the Blood Preoperatively During Hypertensive Crises, Ann. Surg. **106**:85-91 (July) 1937.

8. Evans, V. L.: Suprarenal Tumor with Paroxysmal Hypertension, J. Lab. & Clin. Med. **22**:1117-1120 (Aug.) 1937.

(Footnotes continued on next page)

Brunschwig, Humphreys and Roome,[11] Kremer,[12] Kelly, Piper, Wilder and Walters,[13] MacKenzie and McEachern,[14] and Palmer and Castleman,[15] together with those in the foreign literature, the clinical features of the disease have not been duly stressed. It is for this reason that we are reporting 2 cases of paroxysmal hypertension and emphasizing the manifestations.

REPORT OF CASES

CASE 1.—A white single man aged 27 was admitted to the University Hospitals on Sept. 10, 1938, because of attacks of swelling of the neck of three years' duration. The attacks were more prominent during the fall and winter, but they were induced also in the summer by working in the field. The patient thought that the wearing of suspenders played a role in their induction. The duration of the attacks varied from only a few hours to as long as a day. The usual accompanying manifestations were: a sense of swelling of the neck, a forceful heartbeat which was rarely rapid, throbbing occipital headache, nervousness, sweating, weakness, easily induced fatigue, polyuria and constipation. Occasionally nausea and vomiting occurred, and on only one occasion was shortness of breath noted. Precordial and epigastric distress, cyanosis, air hunger, tingling of the extremities, changes in color of the extremities or nose, vertigo, tinnitus, epiphora, sialorrhea and diarrhea did not occur.

The objective manifestations revealed by examination of the patient on admission were as follows: The patient was a tall, thin man with acromegalic facies. He had several yellowish neuromas of the conjunctiva of each lid, false teeth, a slightly palpable thyroid gland, forceful carotid pulsations with leathery arterial walls, an upper dorsal kyphosis, long, slender fingers and hyperextensibility of the fingers and knees. The heart was of normal size and had an accessible left ventricle; a constant systolic murmur was observed at the apex and the arterial pressure was variable, ranging from 98 to 260 systolic and from 56 to 150 diastolic.

Slight albuminuria was observed. The hemoglobin content of the blood was 13 Gm. per hundred cubic centimeters, and the blood count was erythrocytes 4,420,000 and leukocytes 8,000. The Wassermann reactions of the blood and the spinal fluid were negative. The basal oxygen consumption was 14 per cent below

9. Holst, E. J.: Three Cases of Chromaffin Cell Tumors of the Suprarenal Glands, Acta med. Scandinav. **94**:510-526, 1938.

10. Binger, M. W., and Craig, W. M.: An Atypical Case of Hypertension with a Tumor of the Adrenal Gland, Proc. Staff Meet., Mayo Clin. **13**:17-20 (Jan. 12) 1938.

11. Brunschwig, A.; Humphreys, E., and Roome, N.: Relief of Paroxysmal Hypertension by Excision of Pheochromocytoma, Surgery **4**:361-370 (Sept.) 1938.

12. Kremer, D. N.: Medullary Tumor of Adrenal Gland, with Hypertension and Juvenile Arteriosclerosis, Arch. Int. Med. **57**:999-1002 (May) 1936.

13. Kelly, H. M.; Piper, M. C.; Wilder, R. M., and Walters, W.: Case of Paroxysmal Hypertension with Paraganglioma of Right Suprarenal Gland, Proc. Staff Meet., Mayo Clin. **11**:67-70 (Jan. 29) 1936.

14. MacKenzie, D. W., and McEachern, D.: Tumor of Medulla of Adrenal, J. Urol. **40**:467-476 (Oct.) 1938.

15. Palmer, R. S., and Castleman, B.: Paraganglioma (Chromaffinoma, Pheochromocytoma) of the Adrenal Gland Simulating Malignant Hypertension, New England J. Med. **219**:793-796 (Nov. 17) 1938.

normal. Intrathecal pressures were normal. Tests of the cerebrospinal fluid gave normal readings.

Subsequent Course and Findings.—The paroxysms occurred almost daily, giving an excellent opportunity for the study of the various manifestations. No alterations were produced in the electrocardiogram, but glycosuria, albuminuria, cylindruria and hyperglycemia, with a sugar content as high as 273 mg. per hundred cubic centimeters, developed during a paroxysm. The blood sugar levels at comparable times of the day, without an attack, were 110 to 118 mg. per hundred cubic centimeters. Between attacks the renal urea clearance was 90 per cent of normal, but it was reduced to 53 per cent of normal during an attack. Determinations of the chemical constituents of the blood revealed: urea nitrogen 12.6 mg., creatinine 1.0 mg., serum proteins 6.81 Gm., calcium 10.2 mg. and phosphorus 4.7 mg. per hundred cubic centimeters. The sella turcica was of normal size. A biopsy of the pectoralis major muscle showed normal arteries and arterioles. The cold pressor test failed to produce an attack on two occasions.

Localization of the tumor was difficult. Intravenous and retrograde pyelograms, soft tissue roentgenograms of the adrenal regions and perirenal insufflation of air gave no added information.

The right adrenal region was explored through a posterior approach with the patient under ether anesthesia. A tumor which measured 4 by 6 cm. was found adherent to the adrenal gland and necessitated removal of the gland also. Manipulation of the tumor in situ produced an increase of both systolic and diastolic arterial pressures. The removal of the tumor, however, resulted in a rapid fall in arterial pressures, which was finally checked at 60 systolic and ? diastolic by the subcutaneous administration of epinephrine. The arterial pressures rose gradually to 80 systolic and 50 diastolic by evening, and to 110 systolic and 80 diastolic the following morning, where they remained until the patient's discharge from the hospital three months later. The postoperative course was stormy for the first two days and was further marred by the development of pneumonia, complicated by empyema. In addition to the usual postoperative therapy, large amounts of sodium chloride and 10 cc. of adrenal cortex extract were administered daily for two weeks. Microscopic examination of the tumor revealed that it was a pheochromocytoma.

The possibility that Addison's disease might develop because the right adrenal gland had been removed and the condition of the left adrenal gland was unknown caused us to carry out the procedure recommended by Cutler, Power and Wilder.[16]

The results were within normal limits, and the patient manifested no evidence of adrenal cortical insufficiency three months after the operation.

Case 2.—A white married woman 34 years of age was admitted to the University Hospitals on Nov. 1, 1938, because of inability to walk, high blood pressure and heart trouble. She had not been well for twenty years. There had been many functional complaints, such as severe matutinal pressure headaches, occasional nausea and vomiting and diminution of vision. These symptoms had not increased, but on Aug. 14, 1938, the patient suddenly became unconscious for the first time and remained in this state for about one hour. There were no convulsions. On regaining consciousness she noted a stabbing pain which appeared in the upper part of the left arm and in the left shoulder and radiated to the precordium. This pain persisted until admission. Usually it was a dull ache, but two or three times a week it was aggravated, being on those occasions acute, knifelike and stabbing. At such

16. Cutler, H.; Power, M. H., and Wilder, R. M.: Concentration of Chloride, Sodium and Potassium in Urine and Blood: Their Diagnostic Significance in Adrenal Insufficiency, J. A. M. A. **111**:117-122 (July 9) 1938.

times the face and lips became pale and the breath short and occasionally nausea and vomiting occurred. Abasia had caused the patient to remain in bed since the onset of the symptoms. The previous symptoms became aggravated, and her physician stated that she had high blood pressure and heart trouble.

The objective manifestations revealed by examination of the patient on admission were as follows: The patient was a well developed and well nourished woman. She had congenital bilateral exophthalmos, an interpupillary distance of 83 mm. and hyperplastic otitis media, bilaterally, with acoustic neuritis. The heart was of normal size, with an accessible left ventricle and an accentuated mitral second sound. The arterial pressures were variable, ranging from 146 to 280 systolic and from 88 to 130 diastolic.

Slight albuminuria was noted on several occasions. Chemical analysis of the blood revealed a hemoglobin content of 13 Gm. per hundred cubic centimeters, an erythrocyte count of 4,370,000 and a leukocyte count of 5,300. The Wassermann reactions of the blood and the spinal fluid were negative. The basal oxygen consumption was 23 per cent above normal. Intrathecal pressures were normal, and tests of the cerebrospinal fluid gave normal readings.

Subsequent Course and Findings.—The patient had repeated attacks of paroxysmal hypertension. The usual manifestations during an attack were aching of the feet, cold sweat appearing simultaneously over the entire body, generalized pallor, intense throbbing headache, precordial pain, shortness of breath, extreme fear of death, clonic contractions of the extremities, screaming, agitation, rapid pulse and elevation of arterial pressures. The paroxysms usually increased in intensity until they were terminated by the intravenous administration of sodium amytal (sodium isoamylethylbarbiturate). The electrocardiogram and blood sugar level were unaltered by paroxysms, and glycosuria and albuminuria did not occur. Intravenous pyelograms were normal. Roentgenographic studies of the chest, adrenal regions and gastroenteric tract revealed no abnormalities. The cold pressor test elicited a hyperreaction but did not produce an attack.

Perirenal insufflation of air was not attempted in this case, because it had been unsuccessful in the previous case and alarming symptoms had followed it.

The right adrenal region was explored through a posterior incision with the patient under anesthesia induced by means of avertin with amylene hydrate and cyclopropane. No abnormalities were found. The splanchnic nerve, however, was sectioned, and the first and second lumbar ganglions were removed. The patient's condition was not improved, and one month later the left adrenal region was explored. Although a tumor was not discovered, splanchnectomy and ganglionectomy were performed. The paroxysms of hypertension continued, and hysterical anesthesia of the entire left side of the body developed.

It appeared certain that the patient had a pheochromocytoma, but the two previous surgical procedures had failed to locate it, and two months later the hypertension became persistent. Section of the anterior and posterior roots of the thoracic nerves from the first through the fifth and destruction of the sympathetic tracts at the third thoracic level were decided on instead of an exploratory laparotomy. The arterial pressure declined to 138 systolic and 90 diastolic after the operation, and fluctuated between 110 systolic and 64 diastolic and 154 systolic and 100 diastolic. One paroxysmal attack occurred, two and a half months after the last operation, at which time the arterial pressures reached 195 systolic and 110 diastolic, but accompanying manifestations were mild. The subjective manifestations were almost entirely relieved. The headaches subsided and the vision improved, but a dull precordial distress continued. The patient stated that her health was better than it had been at any time during the past twenty years.

COMMENT

Paroxysmal hypertension is usually curable if it is diagnosed before irreparable vascular damage has occurred. Failure to comprehend the situation is, therefore, extremely unfortunate. The various manifestations described in the literature are listed in the accompanying table. The symptoms, however, are frequently similar to those accompanying functional anomalies. A history of paroxysmal attacks of peculiar sensations may be the only subjective manifestation. These peculiar sen-

Manifestations of Paroxysmal Hypertension Which Have Been Described in the Literature

Subjective	Objective
Neck: a. Fulness; b. Choking; c. Swelling	Pallor followed by flushing of skin
Substernal region: a. Pressure; b. Pain; c. Peculiar feeling	Cyanosis of nail beds
Epigastrium: a. Fulness; b. Pain; c. Burning; d. Peculiar feeling	Angiospasm of extremities and tip of nose
Tingling of extremities	Angiospasm of arterioles of ocular fundi
Blanching of extremities	Hypertension
Blanching of tip of nose	Tachycardia or forceful cardiac impulse
Generalized sweating	Epiphora
Pallor	Sialorrhea
Nervousness	Glycosuria
Tremor	Albuminuria
Muscular weakness	Cylindruria
Palpitation	Hyperglycemia
Air hunger	
Headache	
Tinnitus	
Vertigo	
Epiphora	
Sialorrhea	
Nausea	
Vomiting	
Abdominal colic	
Diarrhea	
Constipation	
Polyuria	

sations may be located in the neck, the epigastrium or the substernal regions. When they occur in the neck, they are described as a sensation of fulness, choking or swelling; in the substernal region they may be identical with those accompanying angina pectoris, or may be only "peculiar sensations"; in the epigastrium they may be described as actual pain or may suggest the possibility of a peptic ulcer. Angiospasm of the extremities and of the tip of the nose during an attack may well be confused with symptoms of Raynaud's disease. Other subjective manifestations which may be present during the paroxysms but are not likely to be elicited unless the possibility of paroxysmal hypertension is considered are sweating, pallor, nervousness, tremor,

muscular weakness, palpitation, headache, nausea, vomiting, vertigo, tinnitus, tingling of the extremities, air hunger, epiphora, abdominal colic and diarrhea. The duration of these paroxysms varies from only a few minutes to as long as twenty-four or forty-eight hours.

The physician is usually consulted between paroxysms at the time when objective manifestations are absent. If an attack should occur in his presence, the objective manifestations which may be observed are as follows: pallor followed by flushing of the skin, sweating, a reddish to a dusky blue discoloration of the finger nails, peripheral angiospasm of the extremities and nose, constriction of the arterioles of the ocular fundi, hypertension, either tachycardia or a slow forceful cardiac impulse, glycosuria, albuminuria, cylindruria and hyperglycemia. It is advantageous, therefore, to observe the patient during an attack. Patients occasionally observe conditions which will produce a paroxysm. Porter and Porter's [17] patient could produce an attack by flexion of the body anteriorly and slightly to the left. Nuzum and Walton's [3] patient noted that exercise before breakfast would initiate an attack, and MacKenzie and McEachern's [14] stated that a blow on the abdomen would precipitate a paroxysm. Other patients know of no precipitating circumstances; therefore, methods for producing an attack are desirable. The injection of epinephrine used by Coller, Field, and Durant,[6] and the cold pressor test used in our cases were both unsuccessful, whereas Nuzum and Walton's [3] method of applying pressure over the carotid sinus was successful. These methods have been used in only a few cases, however, and further observations are indicated.

That paroxysmal hypertension may progress into the persistent variety has been suggested by Wells and Boman [2] and others, and a pheochromocytoma was discovered in a case of persistent hypertension described by Binger and Craig.[10] The condition in our second case progressed into a persistent type, but the patient continued to have paroxysms during which the arterial pressures rose above the basal level. Although the presence of a pheochromocytoma in this patient is doubtful, there is sufficient evidence to indicate that certain patients with persistent hypertension may have had an initial paroxysmal variety, and therefore patients with persistent hypertension should be interrogated concerning previous paroxysmal manifestations.

The presence of a tumor in many of the reported cases has not been difficult to ascertain because of the presence of a palpable abdominal mass. In certain instances of smaller tumors deformities have been visible in the pyelograms. The tumor may be too small, however, to

17. Porter, M. R., and Porter, M. F., Jr.: Report of a Case of Paroxysmal Hypertension Cured by Removal of an Adrenal Tumor, Surg., Gynec. & Obst. **50**: 160-162 (Jan.) 1930.

alter the pyelogram, or it may not be in close proximity to the kidney or even be in the adrenal region. If the pyelograms show no abnormalities, perirenal insufflation of air has been recommended by Mencher [18] and Roome.[19] This procedure has not received general acceptance. Walters and Kepler [20] discontinued its use after three severe reactions had occurred. Fish [21] abandoned the use of air after the occurrence of two fatalities from air embolism, but he stated that the procedure should not be condemned and that since the substitution of oxygen for air there have been no known fatalities. Mencher [18] had no important reactions to it. Alarming reaction occurred in our patient after air insufflation by which the tumor was not visualized. This procedure has definite diagnostic possibilities, and its place as a diagnostic aid cannot be properly evaluated until there are further observations.

If the location of a tumor has not been ascertained by adequate urologic studies, by perirenal air or oxygen insufflation and by careful roentgenographic studies of the mediastinum, it is necessary to explore surgically the adrenal regions. It should be borne in mind, however, that the tumor may arise from aberrant glandular tissue and that therefore it may not be located in the adrenal region.

SUMMARY

The manifestations of paroxysmal hypertension have not been duly stressed. These manifestations and the diagnostic aids are therefore emphasized, and one case of proved and one of doubtful pheochromocytoma are reported.

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18. Mencher, W. H.: Perirenal Insufflation, J. A. M. A. **109**:1338-1341 (Oct. 23) 1937.

19. Roome, N. W.: Visualization of the Adrenal Glands by Air Injection, J. A. M. A. **111**:1061-1065 (Sept. 17) 1938.

20. Walters, W., and Kepler, E. J.: Surgical Lesions of Adrenal Glands, J. A. M. A. **111**:1061-1065 (Sept. 17) 1938.

21. Fish, in discussion on Roome.[19]

CLINICAL VALUE OF DETERMINATION OF CHOLESTEROL ESTERS OF BLOOD IN HEPATIC DISEASE

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The isolation of cholesterol from gallstones and its establishment as one of the characteristic components of the bile by Chevreul [1] focused attention on the changes in cholesterol metabolism in hepatic and biliary disease.

The literature dealing with subsequent studies in cholesterol metabolism has been reviewed by McNee,[2] Campbell,[3] Muller,[4] Epstein,[5] Klein [6] and Hurxthal and Hunt.[7] There is a general agreement that the total cholesterol in the blood may be increased in disease of the biliary tract, especially in obstructive jaundice, whereas in parenchymatous hepatitis there is a fall to subnormal values.

The interpretation of changes in the blood cholesterol in relation to hepatic disease and its use in the differential diagnosis of jaundice are rendered more difficult by the fact that many other disease processes, not necessarily involving the liver, influence the blood cholesterol. Marked changes or variations from the normal are seen in such metabolic

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1. Chevreul, M.: Sur plusieurs corps gras: V., Ann. de chim. (pt. 5) **95**:40, 1815.

2. McNee, J. W.: Cholesterin: An Account of Its Relations to Pathology and Physiology, Quart. J. Med. **7**:221, 1914.

3. Campbell, J. M. H.: Cholesterol in Health and Disease, Quart. J. Med. **18**:393, 1925.

4. Muller, G. L.: The Cholesterol Metabolism in Health and Anemia, Medicine **9**:119, 1930.

5. Epstein, E. Z.: Cholesterol Metabolism in Liver Disorders, Rev. Gastroenterol. **4**:12, 1937.

6. Klein, W.: Ueber die enzymatische Hydrolyse der Cholesterinester des menschlichen Serums, Ztschr. f. physiol. Chem. **254**:1, 1938.

7. Hurxthal, L. M., and Hunt, H. M.: Clinical Relationships of Blood Cholesterol with Summary of Our Present Knowledge of Cholesterol Metabolism, Ann. Int. Med. **9**:717, 1935.

diseases as diabetes mellitus and acute glomerulonephritis or nephrosis, in endocrine disturbances such as hypothyroidism, hyperthyroidism and ovarian disturbances, in infection, regardless of the site, in anemia and in numerous other conditions.

The cholesterol in the bile is present in the free state, while a considerable proportion of that in the blood is present in the esterified form. Epstein,[5] Klein,[6] Hurxthal and Hunt,[7] Thannhauser and Schaber,[8] Sperry,[9] LaRoche and Grigaut [10] and others have advocated the determination of the ratio between the combined cholesterol (esters) and the total cholesterol as a test of hepatic function. They believe a decrease in the normal ratio, that is, a decrease in serum esters, is indicative of parenchymatous hepatic damage. Epstein,[5] Sperry [9] and Paget and Pierrart [11] stated the belief that the ratio of the combined to the total cholesterol is a physiologic constant, which has been determined by these workers, as well as by Bloor [12] and Thannhauser,[13] to be 65 to 75 per cent. A reduction in this proportion is evidence of hepatic damage. Further observations, both clinical and experimental, have shown that purely obstructive lesions of the extrahepatic bile ducts do not significantly change this ratio.

METHOD AND RESULTS OF CLINICAL STUDY

During the past four years we have intensively investigated the clinical value of the ratio of the combined to the total cholesterol. During this time 645 patients with possible disease of the liver or of the extrahepatic biliary tract have been investigated. It is our intention at this time to evaluate the results of this study in the light of the recent contributions by Epstein,[5] Klein,[6] Sperry,[9] Nedswedski [14] and others in an attempt to determine the clinical value of this ratio.

8. Thannhauser, S. J., and Schaber, H. M.: Ueber die Beziehungen des gleichgewichtes Cholesterin und Cholesterinester im Blut und Serum zur Leberfunktion, Klin. Wchnschr. **5**:252, 1926.

9. Sperry, W. M.: The Effect of Dextrose on the Cholesterol Functions of the Blood, J. Biol. Chem. **116**:65, 1936; Concentration of Total Cholesterol in Serum, ibid. **117**:391, 1937.

10. La Roche, G., and Grigaut, A.: Nos connaissances actuelles sur la cholestérolémie et sa signification clinique, Rev. de méd., Paris **54**:223, 1937.

11. Paget, M., and Pierrart, G.: Nouvelle méthode de détermination du rapport esters du cholestérol/cholestérol total dans le sérum ou dans le plasma sanguin, Compt. rend. Soc. de biol. **126**:1206, 1937.

12. Bloor, W. R.: Cholesterol in the Blood, J. Biol. Chem. **24**:227, 1916; Diet and Blood Lipids, ibid. **95**:633, 1932; The Lipoids of the Blood in Diabetes, ibid. **26**:417, 1916.

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We must emphasize that our determinations have been on whole blood rather than on serum, which has been the accepted method in the literature. Therefore, our values will be found lower than the 65 to 75 per cent recorded as characteristic for normal serum. Whole blood was used to reduce the volume of blood required for making these chemical examinations and the numerous other ones required for a study of the blood. The method used was that of Bloor and Knudson.[15]

During the period of study the routine chemical determinations on each patient were those for total and combined cholesterol, icteric index and van den Bergh reaction. After an intensive study and an adequate follow-up period, 598 of 645 patients were found to have no apparent

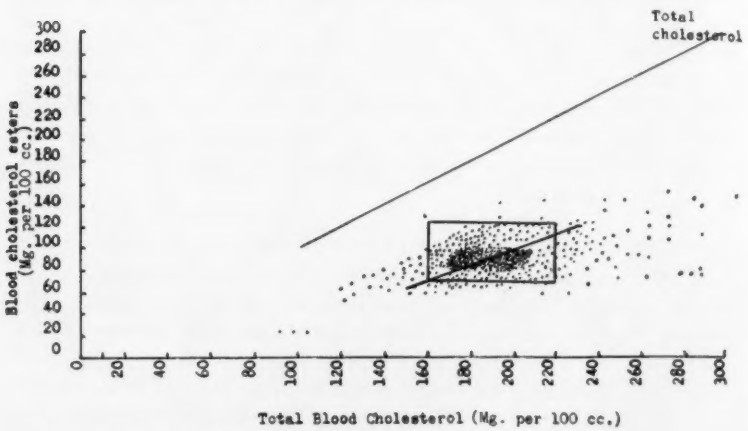

Chart 1.—The range of cholesterol esters in the blood of patients without evidence of hepatic disease or jaundice.

hepatic damage. This represented 92.7 per cent of all patients examined. In this group we found the normal range of total cholesterol to be 150 to 230 mg. per hundred cubic centimeters and that of the esters to be 60 to 120 mg. The ratio of the combined to the total cholesterol was found to be 46 per cent plus or minus 6. This range, shown graphically in chart 1, clearly illustrates the constancy of our determinations. The upper oblique line represents the total cholesterol and the lower line is the median of the ester determinations. When the total cholesterol is much increased, the ratio no longer holds at 46 per cent, for the esters do not increase in proportion to the total cholesterol.

15. Bloor, W. R., and Knudson, A.: The Separate Determinations of Cholesterol and Cholesterol Esters in a Small Amount of Blood, J. Biol. Chem. **27**:107. 1916.

The frequency curves seen in chart 2 show the distribution of the total and combined cholesterol, respectively, in these normal patients. Of all the determinations on patients in this group, 88.2 per cent fell within this ratio. Only 4 per cent of all values for esters were lower than 60 mg. per hundred cubic centimeters. On further analysis it appeared that in only 3 determinations out of 958 was the cholesterol ester: total cholesterol ratio below 40 per cent when the esters were below the level of 60 mg. per hundred cubic centimeters. We believe this to be a remarkable constancy for the ratio, especially in contrast to our results in patients with evident disease of the liver.

When compared with this uniformity in the values found for normal patients, the values for patients with hepatic damage and with clinical

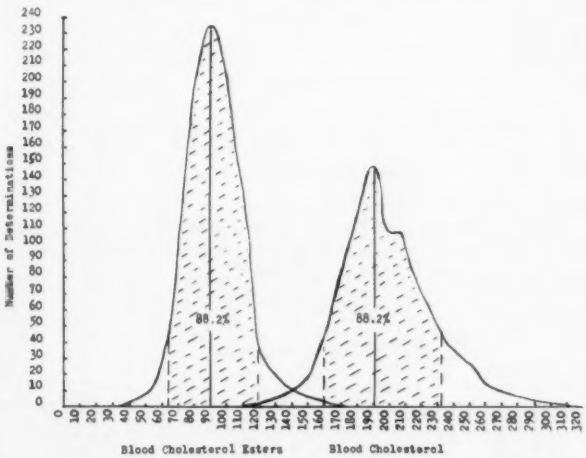

Chart 2.—The frequency curves for cholesterol esters and total cholesterol determinations in the blood of patients without evident hepatic disease.

jaundice showed marked abnormalities in the blood esters and in the ratio of the latter to the total cholesterol (chart 3). Forty-seven patients with proved disease of the liver or with biliary obstruction of extrahepatic origin were examined and studied. One hundred and fifty-four determinations of the total cholesterol and of the cholesterol esters in the blood were made on these patients to ascertain the diagnostic and prognostic value of the test.

Graphically, the results showed that there was a marked "shift to the left" of the values for patients with hepatic disease as compared with those for normal patients. The values for cholesterol esters in the blood of these patients were uniformly lower, and the ratio between the cholesterol esters and the total cholesterol was therefore decreased. In this

group there were 31 patients with hepatic disease. The latter showed the greatest decreases in esters. The esters were not definitely decreased in the 16 patients with obstructive jaundice, although the ratio had a tendency to be lower than the 40 per cent determined as the lower limit for our normal patients. An additional finding in this series was the

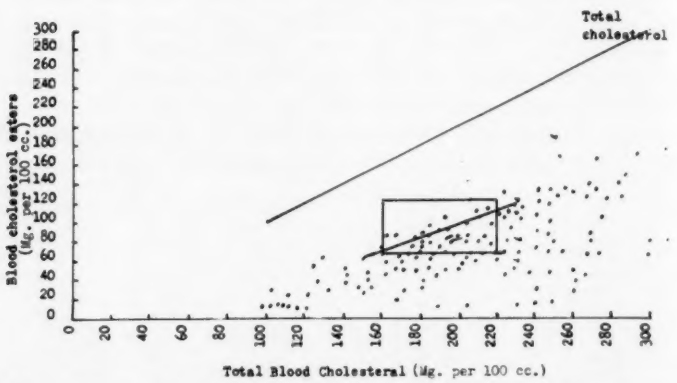

Chart 3.—The range of cholesterol esters in the blood of patients with evident hepatic disease or clinical jaundice. The determinations to the left are predominantly those for patients with intrahepatic disease of the biliary tract, and those to the right, for patients with obstructive jaundice.

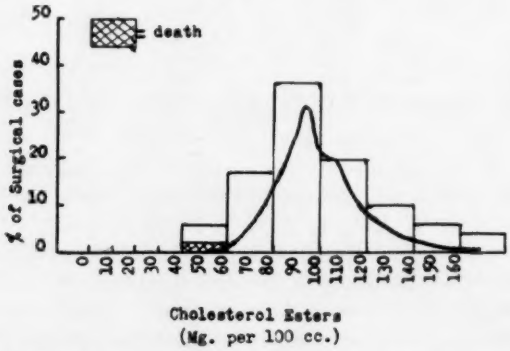

Chart 4.—The cholesterol esters in the blood of surgical patients without evident hepatic disease as contrasted to the frequency curve of normal patients.

general increase of total cholesterol in the blood of patients with obstructive jaundice. No absolute differentiation was possible merely on the basis of this test, for mixed types of jaundice were frequently seen.

Values for Patients on Whom Operations Were Performed.—Included in the general study reported were 92 patients on whom

operations were performed because of cholecystitis or cholelithiasis (chart 4). Seventy had normal physical, blood and operative findings in so far as the liver was concerned. In only 4 of these patients were the values of the cholesterol esters below 40 per cent of the total cholesterol. It is noteworthy that only one death occurred in this group of patients. The remaining 22 patients present an entirely different chemical picture so far as the blood cholesterol esters are concerned. When shown graphically (chart 5), there is a very definite "shift to the left" of the values for the cholesterol esters. All of these patients had jaundice due either to an incomplete extrahepatic obstruction or to definite hepatic injury. The general range for the total cholesterol corresponded to that found in normal patients, but the esters were reduced. Those patients with obstruction but without evident hepatic disease, 13 in number, had

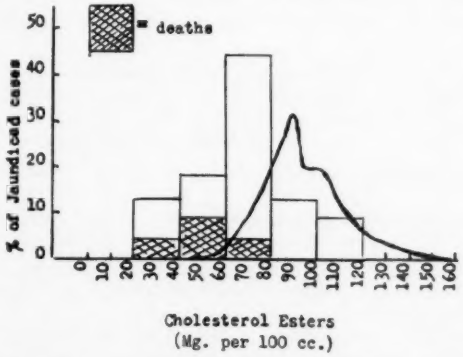

Chart 5.—The cholesterol esters in the blood of patients with jaundice treated by surgical means and their mortality when contrasted with the frequency curve of the esters in normal patients.

no remarkable change in the ester ratio. Those with hepatic damage as seen on biopsy and on operation, showed the greatest shift in this ratio. Four deaths occurred in this select group of patients that had low preoperative blood cholesterol esters.

In the accompanying table these patients are grouped according to the presence of jaundice and the ratio of the esters to the total cholesterol. It is apparent that patients with low cholesterol esters are poor operative risks.

Value of Determination of Cholesterol Esters in Prognosis.—We have found a direct correlation between the values for the cholesterol esters and the prognosis and course of disease in the 47 patients with

evident hepatic damage. These patients fell roughly into two groups, that is, those in whom during the progress of their illness there was a steady increase in the cholesterol esters, and those in whom, in spite of treatment, the esters dropped until only a trace or none was found. In the former group recovery occurred in every instance, while in the latter a fatal termination was the rule. However, we have seen recoveries take place in 2 patients in whose blood only traces of esters were found for periods of ten and twelve days respectively.

Since such determinations do not lend themselves to a statistical study, we are presenting 6 representative case reports with graphs, showing the trend of the blood chemistry determinations. These case reports are representative of the results secured in this study.

CASE 1.—When first seen in June 1932, M. M., a man, gave a history of pain in the upper part of the abdomen and moderate loss in weight. His liver was slightly enlarged, subclinical jaundice was present and his gallbladder was not

The Mortality After Surgical Operations on the Biliary Tract in Relation to the Combined Cholesterol: Total Cholesterol Ratio

	No. Cases	Deaths
No evident hepatic disease or jaundice	70	1
Normal ratio	66	1
Low ratio	4	0
Clinical jaundice or evident disease of the liver	22	4
Normal ratio	13	0
Low ratio	9	4
Total in series	92	5

visualized on roentgen examination. The patient was kept under observation for twenty-one months; during that time ascites developed and his liver became palpable, but he showed no obvious jaundice. He died March 25, 1934, after an exploratory operation, at which time a Talma-Morison operation had been projected. Operation and autopsy revealed advanced hepatic cirrhosis.

Chart 6 shows the reduction in the cholesterol esters in the presence of hepatic damage, even though there was no jaundice or retention of bilirubin in the blood.

CASE 2.—A. P., a white man aged 67, was admitted with a history of jaundice of five weeks' duration. He had fever, evidence of portal obstruction, ascites, a palpable liver and a deepening jaundice. He died three months after admission. Permission for autopsy was not obtained. All clinical evidence pointed to advanced hepatic cirrhosis, probably with an associated cholangitis.

Chart 7 shows the chemical determinations on the blood. It illustrates the prognostic importance of repeated ester determinations, and minimizes the importance of the total cholesterol values. The esters remained low in this patient in spite of a drop in the serum bilirubin and the icteric index.

CASE 3.—S. B., a 26 year old white man, presented himself for hospitalization and gave a history of severe prostration, jaundice, nausea and vomiting of three days' duration after the intravenous injection of 0.6 Gm. of neoarsphenamine.

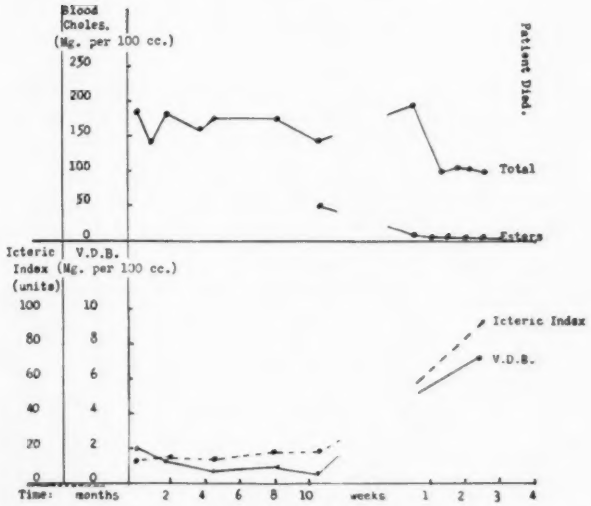

Chart 6.—Chemical determinations on blood of a patient with biliary cirrhosis who died.

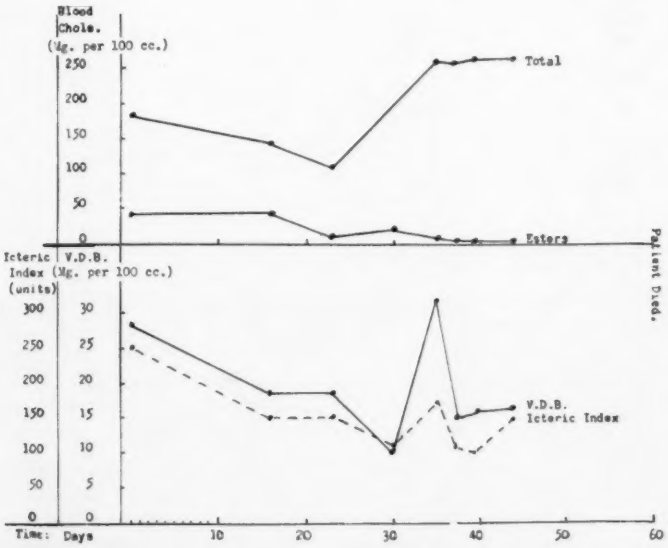

Chart 7.—Chemical determinations on blood of a patient with biliary obstruction who died.

He recovered with the administration of dextrose supplemented by repeated duodenal drainage. The course of the illness indicated that he had a severe toxic hepatitis.

Chart 8 shows the blood chemistry values, which initially presented the picture of a combined obstructive and parenchymatous jaundice. A favorable prognosis was indicated by the early rise in the esters.

CASE 4.—S. H., a woman aged 40, was admitted to the hospital for cholecystectomy in July 1936 with a history of severe jaundice and colic. After operation her jaundice disappeared and the patient became symptom free for two

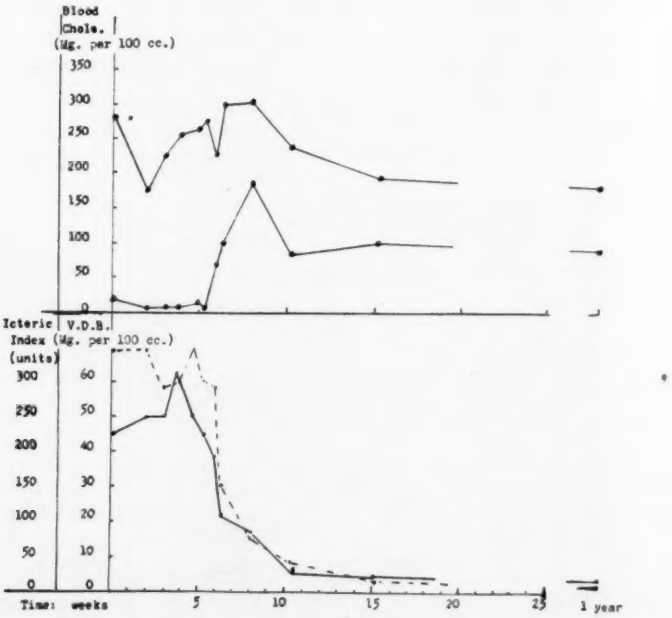

Chart 8.—Chemical determinations on blood of a patient with severe toxic hepatitis who recovered.

months, only to be readmitted for recurrent jaundice in December 1936. At operation stenosis of the common duct, with severe hepatitis, was noted. The patient died of shock (hepatic death?) twenty-four hours postoperatively.

Chart 9 shows how accurately the cholesterol ester values portrayed the true organic state of the liver. In this case, as in the preceding one, the high total cholesterol indicated an obstructive lesion rather than the mixed condition found at operation. The preoperative reduction in the intensity of the jaundice indicated by the icteric index gave a false security to the operative prognosis, which was not warranted by the steady drop in esters or by the pathologic condition found at operation.

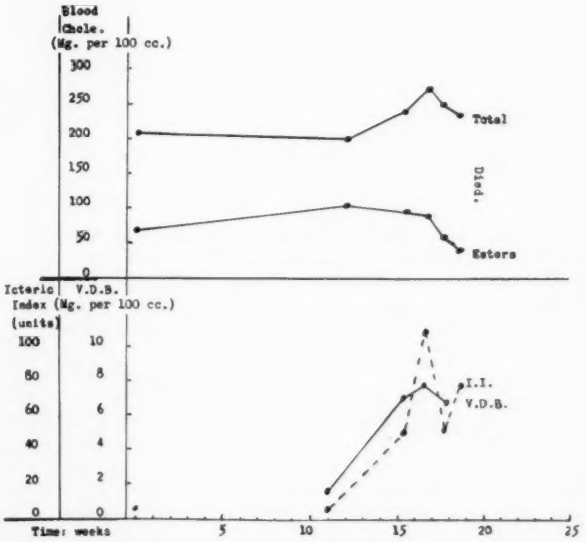

Chart 9.—Chemical determinations on blood of a patient with obstructive jaundice complicated by severe hepatitis who died.

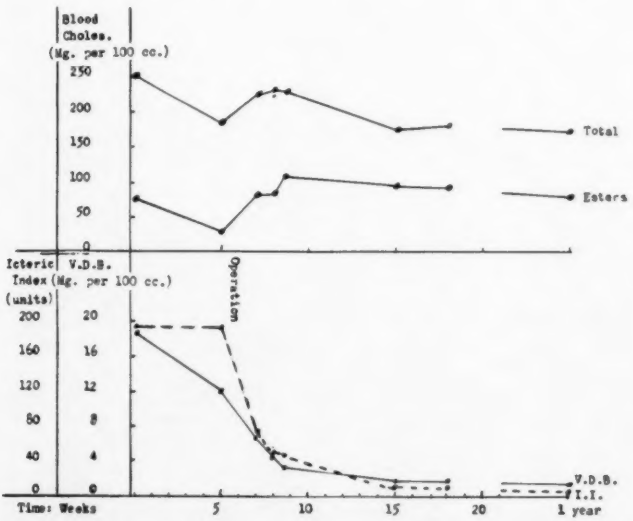

Chart 10.—Chemical determinations on blood of a patient with biliary obstruction who recovered. Note the rise in cholesterol esters as the liver recovered its function.

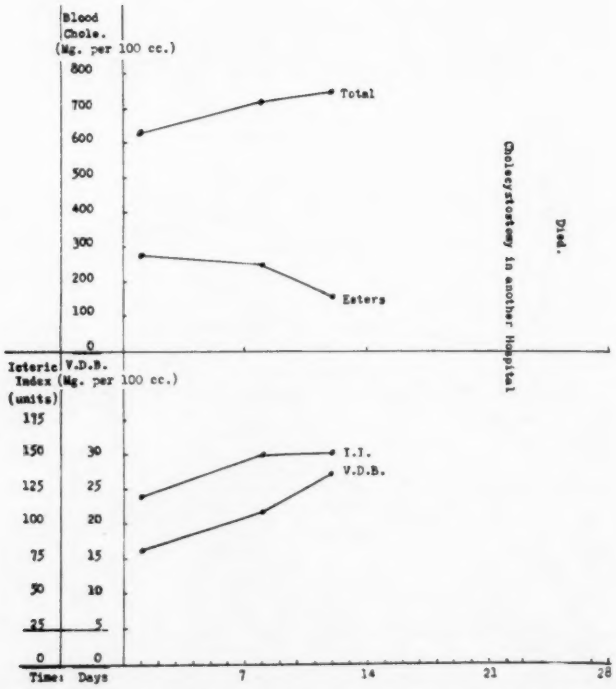

Chart 11.—Chemical determinations on blood of a patient with obstructive jaundice due to carcinoma of the common duct who died.

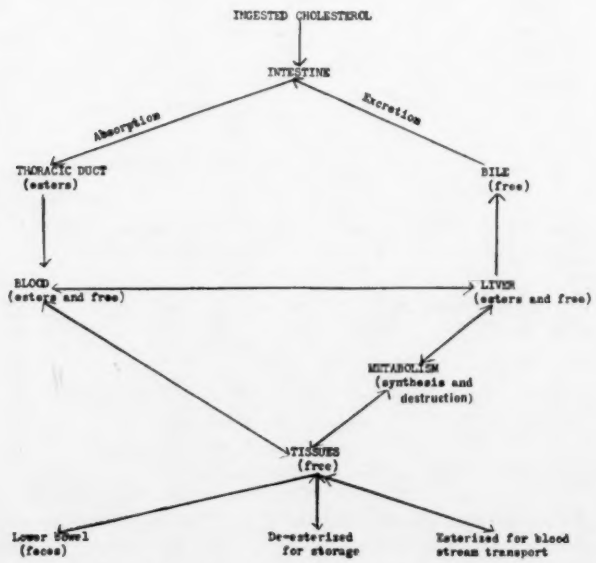

Chart 12.—Present knowledge of cholesterol metabolism.

CASE 5.—A. R., a white woman aged 41, presented herself in September 1937 with a history of jaundice of five weeks' duration, developing shortly after a cholecystectomy. She was dehydrated and had an enlarged liver and severe jaundice. Exploration revealed an enlarged, edematous, obstructed liver with complete atresia of the common duct just below the union of the hepatic ducts. A bilateral hepaticoduodenostomy was done and was followed by recovery.

Chart 10 shows the preoperative impairment of the hepatic function with return to normal on relief of the obstruction.

CASE 6.—I. A., a white man 65 years old, was admitted to the clinic in July 1937, with a history of increasing jaundice, pruritus, mild epigastric pain and loss of weight. He was markedly jaundiced and had a palpable liver, but there were no abdominal masses or tenderness. After study and observation, a diagnosis of carcinoma of the head of the pancreas was made and the patient was referred to his local hospital.

A cholecystectomy was performed Aug. 7, 1937. The operative report read "The liver was intensely swollen and scarred. In the common duct, at the point of entrance of the ductus cysticus, there was a neoplasm which extended well up into the ductus hepaticus." The patient died immediately after operation; no autopsy was reported.

Chart 11 shows the chemical findings, which are characteristic for obstructive jaundice with superimposed hepatic damage. As the obstruction continued, the esters continued to drop. It is unfortunate that terminal studies could not be made on this patient.

DISCUSSION

The general course of cholesterol metabolism may be indicated schematically. The origin of the cholesterol esters in the blood and the regulation of the amount therein is still a source of controversy. That the blood contains an esterifying enzyme has been reported by Huber, Brown and Caset,[16] Riegel, Ravdin and Rose,[17] Vercellone [18] and Klein;[6] the latter also reported that esterification could be produced by extracts of the pancreas, liver, spleen and gastrointestinal tract.

Nedswedski [14] further reported that bile salts were necessary for the esterification of cholesterol, and Chabrol and Sallet [19] have reported parallel changes in the bile salts and cholesterol esters in the blood of

16. Huber, N. J.; Brown, G. O., and Caset, A. E.: Prevention of Cholesterol Arteriosclerosis in the Rabbit by Use of Pancreatic Extract—Lipocaic, Proc. Soc. Exper. Biol. & Med. **37**:441, 1937.

17. Riegel, C.; Ravdin, I. S., and Rose, H. S.: The Effect of Bile With and Without Cholesterol Esters in the Esterification of Cholesterol in Blood Plasma, J. Biol. Chem. **120**:523, 1937.

18. Vercellone, A.: Sulla esterificazione enzimatica delle sterine, Biochim. e terap. sper. **25**:207, 1938.

19. Chabrol, E., and Sallet, J.: L'hypercholestérolémie comme signe de gravite des cirrhoses, J. méd. franç. **26**:280, 1937.

patients with hepatic disease. Sperry [9] and Klein,[6] on the other hand, disagreed; they reported that bile salts inhibit cholesterol esterification.

The importance of the liver in the regulation of cholesterol is disputed by Gardner and Gainsborough,[20] Bürger and Habs [21] and others on the ground that hepatectomized dogs do not lose the power of esterizing cholesterol but actually have an increased ester content in their blood. Klein,[6] however, described the synthesis of cholesterol esters by extracts of the liver. Thannhauser and Schaber [8] and Epstein [5] in particular have insisted that the synthesis of cholesterol esters and the regulation of their level in the blood are a specific function of the liver.

These views are so varied that without more definitive evidence one cannot describe the regulation of the cholesterol esters as a specific and exclusive function of the liver. Our clinical experience is in accord with that previously reported by Thannhauser and Schaber,[8] Epstein,[5] Hurxthal and Hunt,[7] Klein,[6] and others, who indicated that in the presence of hepatic injury the cholesterol esters in the blood are reduced in amount or absent. While a reduction of cholesterol esters is seen more frequently in parenchymatous than in obstructive jaundice, this reduction is of greater value as an indication of the severity of the hepatic damage than as an aid in differential diagnosis.

The determination is of value in indicating an increase in the operative risk, and consequently a poor prognosis, in cases requiring surgical intervention. While from a theoretic standpoint the determination may not be classified as a test of hepatic function, its value from a practical standpoint in the study of patients with hepatic disease has been established.

SUMMARY AND CONCLUSIONS

The value for cholesterol in the blood of adults varies between 150 and 230 mg. per hundred cubic centimeters whereas the combined cholesterol (esters) varies between 60 and 120 mg. The ratio of the combined to the total blood cholesterol is quite constant—between 40 and 52 per cent.

In this series, patients with evident hepatic damage had a decreased amount of combined cholesterol in the blood. This decrease was sometimes but not always associated with a decrease in the total cholesterol. The ratio, per se, was not of as great diagnostic usefulness as was the total amount of esters present in the blood.

In uncomplicated obstructive jaundice the combined cholesterol tends to rise in proportion to the rise in total cholesterol; but in hepatic disease

20. Gardner, J. H., and Gainsborough, H.: Blood Cholesterol Studies in Biliary and Hepatic Disease, Quart. J. Med. **23**:465, 1930.

21. Bürger, M., and Habs, H.: Die alimentäre Hypercholesterinämie beim stoffwechselgesunden Menschen, Ztschr. f. d. ges. exper. Med. **56**:640, 1927.

the cholesterol esters tend to disappear from the blood regardless of the behavior of the total cholesterol.

In a given case a progressive decrease in the values for the combined cholesterol of the blood signifies a poor prognosis, whereas a progressive increase signifies a good prognosis.

The determination of the combined cholesterol of the blood is of great value in determining the prognosis of surgical treatment of patients with disease of the biliary tract.

TREATMENT OF PNEUMONIA WITH SULFAPYRIDINE

OBSERVATIONS ON TOXIC REACTIONS

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Since the appearance, in 1938, of favorable reports [1] on the use of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) in the treatment of pneumococcic pneumonia, attention has been focused on this substance. Agreement on its usefulness has been general, but little mention has been made of the serious toxic manifestations which may attend its use. It is chiefly by reason of the latter fact that we are making a report on a small series of cases.

SELECTION OF CASES

Sulfapyridine became available in this hospital in October 1938,[1a] at a time when we were still engaged in evaluating antipneumococcus rabbit serum in the therapy of pneumonia. This work was continued until mid-December. Until that time, therefore, patients with pneumonia were divided into three groups: those who were being treated with serum, those who were treated with sulfapyridine and controls. This accounts for the small number of patients treated with sulfapyridine up to that time. From mid-December 1938 until mid-February 1939 alternate patients with pneumococcic pneumonia received this drug. After February, in view of the encouraging results seen in our own clinic and those reported by others, it was decided to use sulfapyridine in the treatment of every patient with pneumonia, without reserving any as controls.

In the group of 18 patients with pneumococcic pneumonia treated during the period from October 1938 to February 1939 there was 1

From the Department of Medicine, University of Toronto, and the Medical Service, Toronto Western Hospital.

1. Evans, G. M., and Gaisford, W. F.: Treatment of Pneumonia with 2-(p-Aminobenzenesulphonamido) Pyridine, Lancet **2**:14, 1938.

1a. The sulfapyridine was provided by Messrs. May and Baker, through Poulenc-Frères.

death. The average total dose of the drug was 22 Gm., and it was found that the amount of drug free in the blood ranged from 2.5 to 11.8 mg. per hundred cubic centimeters, the average amount being about 6 mg. It was believed that these amounts were probably lower than the optimum, and therefore it was decided to increase the initial and the total dose so that each patient would receive an average of 35 Gm. of sulfapyridine. It was in the group of patients who received the latter amount that severe toxic manifestations were observed.

In this analysis only those patients are included who were in the hospital over twenty-four hours, had pneumococci in the sputum and

TABLE 1.—*Types of Pneumococci and other Bacteria in Sputum from Ninety Patients Treated with Sulfapyridine (Oct. 1, 1938 to June 1, 1939)*

Organism	Patients	Deaths
Pneumococcus type: I	11	1
II	10	0
III	4	0
V	2	0
VI	2	0
VII	3	0
VIII	3	0
XVI	2	1
XIX	1	1
XX	1	0
Undetermined	30	3
Mixed growths (Bacillus influenzae, Friedländer's bacillus and others)	8	1
Staphylococcus aureus	2	2
Streptococcus hæmolyticus, beta type	9	2
Totals	88*	11

* In the other 2 cases in the group the specimens typed to group C and group D, respectively, but the individual types could not be determined.

In 2 cases Str. haemolyticus was found only by mouse inoculation, a pneumococcus, type not determined, having been present initially.

In each of 2 cases pneumococci, type XXIII and type XXVI, respectively, were found coincidentally with hemolytic streptococci.

received at least 10 Gm. of the drug. Patients with postoperative pneumonia are excluded.

INVESTIGATION

On admission of a patient the history was taken, a physical examination, studies of the blood and a urinalysis were made, and any pneumococci present in the sputum were typed. The diagnosis was confirmed roentgenologically whenever necessary. If the type of pneumonia was not revealed by the Neufeld method, mouse inoculation was done. Bacteriostatic tests in sulfanilamide and sulfapyridine were carried out on organisms isolated from cultures of the sputum.[2] Blood was taken from every patient on admission, and thereafter as indicated,

2. This work was done by Mr. D. O. Scott with the aid of a special grant from the Banting Research Foundation.

for culture. During the administration of the drug daily white cell counts, hemoglobin estimations and urinalyses were made and careful records of the intake and output of fluids were kept. Chemical estimations of the total, free and combined sulfapyridine in blood and urine were made daily throughout this period. Patients whose sputum showed pneumococci of types I, II, III, IV, V, VII, VIII or XIV were given the Francis test with the type-specific polysaccharide (Lederle), until a positive result appeared.

Table 1, giving the types of pneumococci and other bacteria occurring in the sputum of these patients, is based on: (*a*) Neufeld typings to pneumococcus type VIII from July to December 1938, (*b*) Neufeld typings to type XXXII from December 1938 on, and (*c*) mouse inoculations to bring out or confirm types, from February 1939.

THE BACTERIOSTATIC TEST

During the season 1938-1939, when sulfanilamide was tried on a controlled series of patients with type III pneumococcic pneumonia, a variation in the sensitivity of some strains of this pneumococcus to in vitro bacteriostatic tests was noted. It was therefore decided to carry out this investigation with sulfapyridine therapy, in order to discover whether there was any correlation between the clinical results of treatment and such tests.

In all cases in which the etiologic organism could be determined, the test was carried out as follows:

Wright's[3] nutrient broth was used throughout except for the substitution, recently, of some peptones, as suggested by White and Parker.[4] Tubes were set up containing a solution of sulfanilamide or sulfapyridine in broth (from a stock solution containing 100 mg. per hundred cubic centimeters of broth) and sufficient broth added to give drug concentrations of 0.25, 1, 5 and 10 mg. per hundred cubic centimeters. Two drops of a 1:5,000 dilution of an eighteen to twenty-four hour broth culture was used in each tube. The bacteriostatic effect was estimated by the turbidity of the broth after twenty-four hours' incubation at 37.5 C.

Table 2 gives the results of bacteriostatic tests and shows how the minimal effective inhibition concentration varies with the two chemicals and with the various organisms. All the strains of pneumococci isolated were inhibited by both chemicals, but, as the table shows, there was great variation in the minimal concentration necessary to accomplish inhibition. We were unable to find any correlation between the bacteriostatic concentration in vitro and the effective concentration of the drug in the blood. In 1 instance Staph. aureus, and in 2

3. Wright, H. D.: The Importance of Adequate Reduction of Peptone in the Preparation of Media for the Pneumococcus and Other Organisms, J. Path. & Bact. **37**:257, 1933.

4. White, H. J., and Parker, J. M.: The Bactericidal Effect of Sulphanilamide on Beta Haemolytic Streptococci in Vitro, J. Bact. **36**:481, 1938.

instances the beta hemolytic streptococcus, was not inhibited by concentrations of either chemical up to 100 mg. per hundred cubic centimeters.

PLAN OF TREATMENT

Up to February 15, in addition to the routine treatment for pneumonia, each patient received sulfapyridine in approximately the dosage advocated by Evans and Gaisford.[1] An initial dose of 2 Gm. was followed in four hours by another 2 Gm., and then 1 Gm. was given every four hours for six doses. On subsequent days this four-hourly dose was reduced 0.5 Gm. per dose per day. From mid-February the

TABLE 2.—*In Vitro Bacteriostatic Effect of Sulfanilamide and Sulfapyridine on Pneumococci Isolated from Sputum*

	Frequency of Given Minimal Effective Bacteriostatic Concentration									
	Sulfanilamide					Sulfapyridine				
		Concentration, Mg. per 100 Cc.					Concentration, Mg. per 100 Cc.			
Pneumococcus Type	Strains Tested	0.25	1	5	10	Strains Tested	0.25	1	5	10
I	20	6	3	9	2	21	3	3	11	4
II	9	2	3	4	0	9	2	0	6	1
III	14	9	1	3	1	13	6	2	2	3
IV	5	5	0	0	0	5	4	0	0	1
V	4	2	0	1	1	3	0	0	3	0
VI	4	2	0	1	1	4	1	0	2	1
VII	4	0	2	2	0	4	0	0	4	0
VIII	11	4	2	4	1	10	4	2	3	1
IX	2	1	0	1	0	2	1	0	0	1
XII	1	0	0	1	0	1	0	0	1	0
XIII	1	0	0	0	0	1	0	0	1	0
XVI	4	0	1	3	0	4	0	0	1	3
XVII	1	0	0	1	0	1	0	0	1	0
XVIII	2	1	1	0	0	2	1	0	1	0
XIX	1	1	0	0	0	1	0	1	0	0
XX	4	1	0	2	1	4	1	0	2	1
XXII	1	1	0	0	0	1	0	1	0	0
XXIII	2	1	0	0	1	2	1	0	0	1
XXVIII	1	0	0	1	0	1	0	0	1	0
XXIX	2	1	1	0	0	2	1	1	0	0
Not determined	10	7	1	2	0	10	3	5	2	0

doses were at four-hourly intervals but started with 2 Gm. for six doses, then 1.5 Gm. for six doses, then 1 Gm. for six doses, and finally 0.5 Gm. for six or more doses, to complete the course. This amount (at least 30 Gm.) was given unless serious toxic manifestations occurred, in which case the drug was discontinued. Fluids were limited to 2,500 cc. per twenty-four hours during the chemotherapy.

CLINICAL EFFECTS

After the ingestion of the first and second doses of sulfapyridine most patients began to feel more uncomfortable. The great majority experienced nausea and vomiting (see under "Toxic Manifestations"). If they persisted in taking the drug, there was usually a drop in temperature, pulse and respirations to normal within thirty-six hours.

This was maintained in 90 per cent of the patients, the remainder showing a rise in temperature and pulse after the course of treatment had been completed. This commonly indicated the onset of pleural effusion. During the afebrile period, while they were still receiving the drug, the patients suffered none of the distressing symtoms usually associated with pneumonia. They complained instead of the faintly bitter taste which the drug produces in the mouth, of the nausea and vomiting and, in a considerable number of cases, of profound exhaustion and weakness, which passed off when the treatment was completed.

COMPLICATIONS

Pneumococcic bacteremia was noted in 4 of the patients treated with sulfapyridine; all recovered.

Pleural effusion was noted in 8 patients with pneumococcic pneumonia, in 4 of whom it became purulent. Extension of the sulfapyridine therapy in the 4 remaining patients reduced the temperature once more, and the signs of effusion disappeared. A short summary of the 4 cases in which empyema developed follows:

CASE 1.—Miss M. R., aged 17, was admitted to the hospital on Dec. 17, 1938. Pneumonia of the lower lobe of the right lung was well established. A serous pleural effusion was also present on the right side, and from it type I pneumococci were cultured. Repeated aspirations and sulfapyridine therapy failed to control the effusion, and the fluid gradually became purulent. On Jan. 5, 1939 closed drainage was initiated. This was later converted to open drainage. Several courses of sulfapyridine therapy were given and were poorly tolerated owing to the distressing nausea and prostration which were produced. In all, 63.5 Gm. was given. Several transfusions were necessary to offset the severe secondary anemia which gradually developed. The patient made a slow recovery.

CASE 2.—Mr. R. B., aged 22, was admitted on March 3, 1939 and was discharged on May 3. On admission there was pneumonia of the lower lobe of the right lung, with type III pneumococci in the sputum. A right pleural effusion developed, which later became purulent in spite of repeated aspirations and the administration of 48 Gm. of sulfapyridine. Hemolytic streptococci alone grew from the purulent pleural effusion. Open drainage was performed on April 6, and a good recovery was made.

CASES 3 and 4.—Both W. W. and W. S., aged 51 and 21, had type III pneumococci in the sputum, and pleural effusion developed in both. Staph. aureus of the hemolytic type and pneumococcus type III were cultured from the effusion. These organisms were inhibited in vitro only by concentrations as great as 100 mg. of sulfanilamide or sulfapyridine per hundred cubic centimeters. These patients received 45 and 50 Gm. of the drug, respectively, and the pleural effusions were repeatedly aspirated but finally required open drainage. Both patients made good recoveries.

TOXIC MANIFESTATIONS

This is primarily a report on 70 patients who were treated for pneumococcic pneumonia with sulfapyridine, but conclusions as to the

toxicity of this drug may be properly drawn from a consideration of all the patients so treated. The following remarks are therefore based on the results in the 90 patients who received the drug. Eighty-five per cent of these patients suffered some toxic manifestations.

Mild Toxic Manifestations.—1. Nausea and Vomiting. Nausea occurred in 80 per cent and vomiting in 78 per cent of the 90 patients. In about 10 per cent the vomiting became a serious obstacle to adequate treatment. Among the many unsuccessful means used in the attempt to overcome this troublesome symptom were: a powdered form of the drug, given in fruit juice or milk; antacids; a duodenal tube for administering the drug and food.

There are grounds for believing that the nausea and vomiting may be due in part to the local irritation set up by the drug in the stomach. Some patients vomit the tablets a few minutes after swallowing them. On the other hand, patients treated by intravenous injection of the sodium salt of sulfapyridine not infrequently experience nausea and vomiting. This suggests that at least part of this toxic manifestation originates from the central nervous system. Trial of ascorbic acid to control this symptom was unsuccessful. Nicotinic acid has been shown [5] to be effective in controlling the sickness following high voltage roentgen therapy. One of us (W. H. B.) found that the anorexia, nausea, vomiting and depression and to some extent the cyanosis were often remarkably diminished by oral administration of 100 to 300 mg. of nicotinic acid in each twenty-four hours. (This was an independent observation. Priority, however, belongs to Dr. A. P. McGinty, whose work has since come to our notice.[6]) Since March 1939 nicotinic acid has been given in divided doses (50 mg. every four hours) to alternate patients receiving sulfapyridine. Twenty patients have been treated in this way; of these, 12 were nauseated and 8 vomited, but the severity of each symptom has been much less than in the controls of this group or in the series as a whole. Anorexia, in particular, seems to be much less severe in the patients receiving nicotinic acid. The results are sufficiently encouraging to warrant further trial.

Just how nicotinic acid acts in this connection is not yet fully understood. It has been found [7] that pellagrins have an excess of porphyrin in the urine, which has been reduced to normal by the administration of nicotinic acid. However, it would seem from recent work by Graham [5] that the degree of radiation sickness and of the response to nicotinic acid

5. Graham, J. W.: Radiation Sickness: Treatment with Nicotinic Acid, J. A. M. A. **113**:664 (Aug. 19) 1939.

6. McGinty, A. P.; Lewis, G. T., and Holtzclaw, M. R.: Symptoms Occurring with Sulfanilamide Relieved by Nicotinic Acid, J. M. A. Georgia **28**:54, 1939.

7. Spies, T. D.; Cooper, C., and Blankenhorn, M. A.: The Use of Nicotinic Acid in the Treatment of Pellagra, J. A. M. A. **110**:622 (Feb. 26) 1938.

are not related to porphyrin excretion. After the work of Rimington[8] on the pigment metabolism after administration of sulfanilamide and related compounds, Graham suggested that in radiation sickness the abnormal porphyrin excretion is due to disturbance of hemopoietic or of hepatic function. This may be the case also with sulfapyridine, and further studies on this problem are necessary.

At the suggestion of Dr. Alexander Fleming and his associates at St. Mary's Hospital, London, we have since tried giving sulfapyridine as an emulsion (1 Gm. of the powdered drug suspended in 1 drachm [3.88 Gm.] of half strength mucilage of tragacanth B. P.) and have obtained better results than any obtained hitherto. Since we believe that the nausea and vomiting are of both central and local origin, we advise combining the administration of the drug in the form of an emulsion in mucilage of tragacanth with the administration of 30 to 50 mg. of nicotinic acid for each dose of emulsion.

2. Anorexia. This symptom without nausea and vomiting was observed in 4 patients but seemed of no consequence except that it made the patients loath to take the drug. It was alleviated by the use of nicotinic acid.

3. Headache. This is an uncommon symptom. It does not seem to occur with much greater frequency than in patients whose pneumonia is treated symptomatically.

4. Dizziness. This occurred in 6 patients but was not serious.

5. Cyanosis. This symptom was present in 8 patients. In 1 instance, sulfhemoglobinemia was detected spectroscopically. This condition occurred when the level of the free drug in the blood was 14.9 mg. per hundred cubic centimeters.

6. Facial twitching. This symptom was noted in 3 patients. It occurred when the level of the free drug in the blood was high, about 15 mg. per hundred cubic centimeters, and was not of any special significance.

Serious Toxic Manifestations.—The following symptoms were considered indications for either partial or complete withdrawal of the chemotherapy:

1. Oliguria. Oliguria was considered to be present when less than 300 cc. of urine was excreted in twenty-four hours. This complication developed in 9 cases. In these the administration of the drug was

8. Rimington, C., and Hemming, A. W.: Porphyrinuria Following Sulphanilamide: Sulphanilamide Dermatitis, Lancet **1**:770, 1938. Rimington, C.: Disturbance of Pigment Metabolism Following Administration of Drugs of the Sulphanilamide Series and Simpler Related Substances, Proc. Roy. Soc. Med. **32**:351, 1939.

discontinued, and fluids were given in large amounts by mouth and intravenously.

2. Anuria. This symptom occurred in 3 patients.

Mr. H. F., aged 77, had bronchopneumonia at the base of the left lung with pneumococci (the type of which could not be determined) in the sputum. During the course of treatment and in spite of efforts to combat developing oliguria by forcing fluids, he suffered a sharp drop in the white cell count and in hemoglobin, gross hematuria and, later complete anuria. The level of the free drug in the blood was 16 mg. per hundred cubic centimeters. As a result of intravenous administration of fluids and complete withdrawal of the drug, this man made a gradual recovery, no renal impairment being demonstrable.

Mr. J. R., aged 58, was admitted March 9, 1939 and died April 1, 1939. On admission he had bronchopneumonia of the right lung with pneumococci (type not determinable) in the sputum. (Cultures from the lung at autopsy showed hemolytic Staph. aureus.) He was given 23 Gm. of sulfapyridine and he became afebrile in four days. The temperature rose again and a second course of the drug was given (48 Gm. in fourteen days). On the fourth day of this course a macular rash developed, which disappeared without special measures except the interruption of chemotherapy for one day. While he was still receiving the drug (6 Gm. daily) oliguria developed (210 cc. of urine in twenty-four hours); then, for a short time, he was anuric. Fluids relieved the condition, and the administration of the drug was continued (3 Gm. daily). Several days later the white cell count was 2,000, and the administration of sulfapyridine was discontinued. In spite of intravenous administration of fluids, blood transfusions and intramuscular injections of liver extract, the white cell count fell to 700, and agranulocytosis was present. Autopsy showed lobar pneumonia, coronary sclerosis, arteriosclerotic kidneys, slight atrophy of the pancreas and a fatty liver.

Mr. W. P., aged 19, was admitted April 16, 1939 and died April 19, 1939. Pneumococci (type XXIII) were found in the sputum, and later, after mouse inoculation, hemolytic Staph. aureus was identified. Sodium sulfapyridine was administered intravenously to a total of 15.2 Gm., and complete anuria developed during the last ten hours of life.

The significance of the oliguria is discussed, and the details of the case of W. P. are reported, elsewhere.[9] Briefly our experience led us to the conclusion that the use of heavy doses with restriction of the fluid intake is a procedure seldom justified, and one attended by serious risks.

3. Gross hematuria. In 6 patients gross hematuria occurred, associated in 4 with pain in the costovertebral angle. The concentration of the free drug in the blood of these 6 patients varied from 10 to 27 mg. It may be that the hematuria is due to precipitation of crystalline sulfapyridine in the renal tissue, as these crystals are not infrequently seen in the urine when concentrations of the free drug are high. In none of these patients was impairment of renal function detected subsequently.

4. Leukopenia. A white cell count of less than 4,500 was recorded for 8 patients. Of these, J. R., already referred to, was the only one in

9. Brown, W. H.; Thornton, W. B., and Wilson, J. S.: Observation on the Absorption, Distribution and Excretion of Sulphapyridine, Dagenan or M. & B. 693, J. Clin. Investigation **18**:803, 1939.

whom the condition resulted in a fatality. Leukopenia was found in patients showing 3 to 11 mg. of the free drug per hundred cubic centimeters of blood. In all these patients there was relative granulopenia, and in the patient whose condition ended fatally agranulocytosis developed.

5. Anemia. Six patients had a sharp drop in hemoglobin and in red cells during the five days of treatment. The average drop in hemoglobin was 14 per cent, and the average decrease in red cells was 700,000. No special measures were adopted to remedy this condition, and recovery was spontaneous. (Details of the blood dyscrasias are given elsewhere.[10])

6. Cutaneous rashes. A fine macular to morbilliform rash developed in 6 patients. One of these was J. R., already referred to, who had a rash two weeks before death. Another, W. L., aged 31, was admitted on Feb. 9, 1939, with pneumonia of the lower lobe of the right lung and type III pneumococci in the sputum. He was much nauseated by the sulfapyridine, and on the fourth day of therapy a maculopapular rash and cyanosis developed. He made a good recovery and returned to work, but he was readmitted on March 3, 1939, again with pneumonia of the lower lobe of the right lung. The sputum contained type V pneumococci on this occasion. A scarlatiniform rash developed on the third day of chemotherapy, and there was a sharp drop in hemoglobin and red cells. Cessation of the therapy and forcing of fluids brought about a disappearance of the toxic manifestations, and the patient made a satisfactory recovery.

7. Thermal reactions. In a few instances withdrawal of the drug apparently resulted in a reduction of the temperature a point or two, to normal. It was difficult to ascertain whether the fever had been due to the drug because the drop in temperature usually occurred about the eighth day of the pneumonia and may have been due to the fact that the febrile phase of the illness happened to cease on that day. There were, however, 5 instances in which a fever frankly due to the effect of the drug was encountered.

8. Mental changes. Some patients seemed to become more restless and confused during treatment with sulfapyridine. It was difficult to determine the cause of extreme drowsiness or of delirium, as such manifestations are common in severe pneumonic conditions; but in 4 fatal cases there was a question of whether these states had been accentuated by treatment, especially since the levels of the drug in the blood were high.

10. Morgan, J. R. E., and Detweiler, H. K.: Hematologic Study of Seventy-Six Pneumonia Cases Treated with Sulfapyridine Including a Fatal Case of Agranulocytosis, J. Lab. & Clin. Med. **25**:275, 1939.

Table 3 is designed to show the relation of toxic manifestations to the total dose of sulfapyridine. Nausea and vomiting are omitted from the list of symptoms because the incidence of these symptoms was reduced by the use of nicotinic acid.

Concentrations in the Blood.—The average maximum blood level of the free drug was about 9 mg. per hundred cubic centimeters. In patients recovering the levels ranged from 3 to 25 mg. In those who died the levels ranged from 5.8 to 28.3 mg. A detailed study of the absorption and distribution of the drug in the tissues has been published elsewhere.[9]

Intravenous and Intramuscular Sulfapyridine Therapy.—In February 1939 supplies of sodium sulfapyridine (Calco) were obtained through Dr. Perrin Long, of the Johns Hopkins Hospital. Later,

TABLE 3.—*Relative Frequency of Serious Toxic Manifestations with Two Schemes of Dosage of Sulfapyridine*

	Lower Doses (Average Total 22 Gm.)	Higher Doses (Average Total 35 Gm.)
Average free drug in blood, mg. per 100 cc.	7	10
Patients	21	69
Number with given toxic manifestations		
Oliguria	0	9
Anuria	0	3
Gross hematuria	1	5
Leukopenia	2	6
Agranulocytosis	0	1
Anemia	0	6
Rash	1	5
Fever	1	4
Deaths	2	9

sodium sulfapyridine was supplied by Poulenc-Frères for intravenous use. Patients treated by the intravenous method are reported on in detail elsewhere.[9] Our experience has as yet been limited, but it would seem that this method of administration should be used only when patients cannot be treated by mouth. When patients were very ill, treatment was begun with an intravenous injection of 70 cc. of a 5 per cent solution (3.5 Gm.). This was later supplemented by further intravenous medication at eight hour intervals or by oral therapy every four hours. The dosage was carefully controlled by clinical and laboratory observations, including chemical estimations of levels of the free drug in the blood. For intravenous use a 5 per cent solution of the drug supplied by Poulenc-Frères was made up with distilled water from the ampules, which contained a 33 per cent solution. For intramuscular use we injected initially 6 cc. of the 33 per cent solution (2 Gm.), directly into the gluteal muscles. This was followed in eight hours by an injection of 1 Gm. into the opposite hip, and a similar dose was given at eight hour intervals until the level of the free drug in the blood was 8 mg.,

or until the patient could take sulfapyridine by mouth. The 33 per cent solution had a p_H of approximately 11.3, and it was remarkable that no great discomfort was occasioned by the injection into the gluteal muscles. An explanation for this may be the small size of the molecule of sodium sulfapyridine.

MORTALITY

Five of the 70 patients who were treated with sulfapyridine died, giving a mortality rate of 7.1 per cent. The following brief summaries will serve to show the type of case in which this chemotherapy was unsuccessful.

1. Mrs. G. T., aged 60, was admitted on Dec. 30, 1938 and died on Jan. 20, 1939. This woman had bilateral bronchopneumonia, with type XVI pneumococci in the sputum, associated with diabetes mellitus and hypertensive cardiovascular disease. Despite the administration of 24 Gm. of sulfapyridine, with the blood levels reaching 11 mg. per hundred cubic centimeters, she never became afebrile. In vitro, the type XVI pneumococcus isolated from the sputum showed bacteriostasis in the presence of 5 mg. of drug per hundred cubic centimeters. At autopsy marked congestion of the lower lobes was noted, but the pneumonia had resolved. There were areas of infarction in the liver and spleen, and a uterine abscess was found.

2. Mrs. H. V., aged 75, was admitted on March 13, 1939 and died on March 29, 1939. The diagnosis on admission was bronchopneumonia of the lower lobe of the right lung, for which she was given sulfapyridine in the routine doses described, so that a blood level of 14 mg. per hundred cubic centimeters was reached. She did not become afebrile. There were pneumococci (type not determinable) in the sputum. Despite continued chemotherapy this pneumonia did not resolve, and the patient died without extension of the disease or development of any complication. At autopsy diffuse bronchopneumonia of the lower lobe of the right lung was noted, together with fibrosis of the heart, acute ulcers of the stomach and moderate fatty degeneration of the liver.

3. Mr. G. B., aged 63, was admitted on March 14, 1939 and died on March 23, 1939. This man had parkinsonism and bilateral bronchopneumonia. The blood levels of free sulfapyridine reached 14 mg. per hundred cubic centimeters with the regular dosage described, but the patient's course was steadily downward. Autopsy revealed marked engorgement of the lower lobes of both lungs and moderate fatty change within the liver. There was marked sclerosis of many blood vessels, especially of the aorta.

4. Mr. H. W., aged 70, was admitted on March 17, 1939 and died on March 23, 1939. This man was admitted to the hospital with a fractured pelvis, and three days later bronchopneumonia developed. This did not respond to 33 Gm. of sulfapyridine, although the blood levels of the drug reached 10.4 mg. per hundred cubic centimeters. Supportive therapy and oxygen were of no avail. Permission for autopsy was refused.

5. Mr. C., aged 70, was admitted on April 21, 1939 and died on April 30, 1939. Bronchopneumonia of the lower lobe of the right lung was present on admission, and pneumococci (type XXVI) were found in the sputum. In spite of the administration of 17 Gm. of sulfapyridine, his condition grew steadily worse, the pneumonic signs persisted and the patient died. Permission for autopsy was refused.

Attention is called to the fact that the average age of those who died was 68 years; none were under 60 years of age.

NONPNEUMOCOCCIC PNEUMONIAS TREATED WITH SULFAPYRIDINE

There were 15 patients in this group, of these, 6 died. The organisms found were distributed as follows:

	Patients	Number Who Died
Mixed: Friedländer's bacillus, etc.	6	1
Hemolytic streptococci of the beta type	6	2
Hemolytic Staph. aureus	3	3

One of the patients who died from pneumonia caused by the beta hemolytic streptococcus deserves special mention.

Mr. R. Y., aged 19, was admitted on March 13, 1939 and died on March 23, 1939. He had a well developed pleural effusion on the right side; beta hemolytic streptococci were cultured. Repeated aspirations and the administration of 33 Gm. of sulfapyridine (level of free drug in the blood, 18.9 mg. per hundred cubic centimeters), failed to control the process. The pulse became very rapid, and the blood pressure fell in spite of stimulants. The patient died two days after an open drainage of the pleural cavity. Permission for autopsy was refused.

COMMENT

Our experience with the use of rabbit serum had previously led us to the conclusion that it has a definite place in the treatment of pneumonia.[11] The death rate among patients treated with serum up to the time of writing has been 10 per cent, as compared with a rate of 25 per cent in the control group over a period of five years. This rate is not significantly different from that among patients treated with sulfapyridine, as here reported. It must, however, be remembered that in our hands the use of serum has been applicable to only about 50 per cent of all patients with pneumonia, whereas sulfapyridine, by virtue of its polyvalency, was used in a much wider field. There can be no question of its value in the treatment of all types of pneumococcic pneumonia. Of outstanding importance is the time saved, because this form of specific treatment can be begun while one is waiting for bacteriologic identification of the causal organism. This is especially apparent in those cases in which sputum is not immediately available.

A definite statement as to the optimum concentration of sulfapyridine in the blood cannot as yet be made, but in general an initial level of 6 mg. per hundred cubic centimeters and a maintenance level of 3 to 4 mg. should be the goal. Patients were encountered whose treatment

11. Kinsey, H. I.; Brown, W. H., and Feasby, W. R.: Antipneumococcus Serum Treatment of Pneumonia, Canad. Pub. Health J. **31**:56, 1940.

had to be discontinued after the first day because of the toxicity of the drug. Some of these made an uneventful recovery without further treatment. In others (particularly those with pneumonia caused by pneumococcus type III) the disease could not be controlled unless high concentrations were established. Resistant conditions could not be determined by reference to bacteriostatic tests as stated in an earlier section of this paper. From October to February, a period during which the modified Evans and Gaisford dosage was used, 2 deaths resulted in 21 patients. In 18 of these the pneumonia was pneumococcic, and 1 of these patients died. After this time larger doses were used, without any improvement in the mortality rate. Among the 21 routinely treated patients in the control series there were 4 deaths.

Undoubtedly the biologic factor (the state of the immunity mechanism) has a very important role in determining how much chemotherapy should be employed and for how long. It was hoped that the Francis test would throw some light on this problem. In a few cases it was of definite aid in demonstrating that an excess of circulating antibodies was present; and in these cases discontinuance of the drug was not followed by exacerbations. The usefulness of this test was unfortunately obscured by the high percentage of positive results obtained on patients at the time of admission to the hospital. Agglutination tests were not used in this investigation; but it seems reasonable to anticipate that a test indicating the time at which the biologic immunity has become fully mobilized would prove to be of very considerable aid in chemotherapy. In any event, the importance of active immunity should not be lost sight of in the treatment of pneumonia. It is our belief that sulfapyridine is of extraordinary value in that it permits treatment to be instituted at once; when the pneumococcus is identified, serum may be used as an adjuvant. Such a method, in which the total dose of sulfapyridine is reduced, may well prove to be the one of choice.

During the period of moderate dosage (October to February) few serious effects were observed, despite the fact that in 2 cases chemotherapy was prolonged. After this period, and coincidental with the institution of more intensive dosage, higher levels of the free drug in the blood were attained, and the occurrence of serious toxic effects became frequent. Hematuria, oliguria, anuria, leukopenia, rashes and fever, which were previously infrequent or not observed, now appeared. This series stands in contrast to almost all those already published in the large number of toxic manifestations observed. On the other hand, the mortality rate noted here is slightly higher than many of those reported elsewhere. The conclusion is inescapable that the high blood levels reached in the latter part of the season did not offer a better protection against death from pneumonia and that the occurrence of serious and

frequent toxic manifestations was directly due to the adoption of heavier doses. The average total and daily doses in the earlier period were, respectively, 22 and 5.5 Gm.; those in the later period were 35 and 7.5 Gm. These small differences emphasize the narrowness of the range between doses which are effective and those which are attended by risk of serious toxicity.

SUMMARY

1. The treatment of pneumococcic pneumonia with sulfapyridine resulted in this series in 5 deaths in 70 patients. The average age of those who died was 68 years.

2. Sulfapyridine therapy did not reduce the incidence of complications of pneumonia in this small series.

3. In this series 85 per cent of 90 patients who received the drug had toxic manifestations. The earlier dosage (average total dose, 22 Gm.) was relatively innocuous, but the later dosage (average total dose, 35 Gm.) was attended by many serious toxic manifestations, without lowering of the death rate. Until more is known of the concentration of sulfapyridine in the blood which is effective in combating pneumococcic pneumonia, heavy doses should be employed with great caution.

4. Nicotinic acid was found to be effective, to some extent, in controlling the nausea and vomiting which occurred in 85 per cent of the patients receiving sulfapyridine. Vomiting was also reduced when the drug was given as an emulsion, the powder suspended in mucilage of tragacanth.

5. The reduction of the fluid intake to less than 2,500 cc. when heavy doses were employed was observed to cause acute renal insufficiency, resulting in oliguria and anuria.

6. No correlation between in vitro bacteriostatic tests and clinical results with sulfapyridine could be shown.

7. Sulfapyridine was unsuccessful in the treatment of streptococcic and staphylococcic pneumonia.

PURPURA HAEMORRHAGICA FOLLOWING NEOARSPHENAMINE AND BISMARSEN THERAPY

FURTHER STUDIES ON SENSITIVITY TO ARSPHENAMINE AND TOLERANCE TO MAPHARSEN

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In 1936 studies on 3 patients with purpura haemorrhagica following neoarsphenamine therapy were reported.[1] We ascertained by experiments that 2 of these patients were very sensitive to neoarsphenamine but apparently not sensitive to mapharsen, as the intravenous injection of this arsphenamine derivative failed to produce any significant effects on the platelets and capillaries or any untoward constitutional reaction. The third patient of the series disappeared from observation after leaving the hospital; hence no experimental studies were made.

Since publication of the report mentioned, we have had an opportunity to study 6 additional patients who showed hemorrhagic phenomena following the therapeutic use of arsphenamine derivatives. It appeared to us important to record our experimental studies on these patients, particularly those on 5 patients of the series who showed typical purpura haemorrhagica following the use of neoarsphenamine or of bismarsen but who had no apparent reaction following the intravenous injection of mapharsen.

Since our 1936 report and up to the time of the present report (March 1939), we have found recorded only 3 instances of thrombopenic purpura following arsphenamine therapy. In the Soviet Russian medical literature, Izhevskiy [2] in 1936 reported 1 case in which the condition followed neoarsphenamine therapy. In 1937, Marín and Tettamanti [3] reported 1 case in which it followed the fourth injection of 0.18

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1. Falconer, E. H.; Epstein, N. N., and Wever, G. K.: Purpura Hemorrhagica Following the Administration of Neoarsphenamine, Arch. Int. Med. **58**:495 (Sept.) 1936.

2. Izhevskiy, K. M.: Hemorrhagic Purpura Following Arsphenamine Therapy, Klin. med. **14**:1053, 1936.

3. Marin, J. V., and Tettamanti, J. C.: Hemorrhagic Purpura Due to Arsphenamin Therapy, Rev. méd. del Rosario **27**:127 (Feb.) 1937.

Gm. of sulfarsphenamine. In the Danish medical literature, Stigaard [4] reported the case of a young man with thrombopenic purpura following prolonged treatment with neoarsphenamine.

The present report concerns studies on 5 patients, 2 with thrombopenia and purpura following intravenous injection of neoarsphenamine and 3 showing similar phenomena after intramuscular injections of bismarsen. Another patient is included in this study because she had a somewhat different type of reaction to the arsenicals, showing large ecchymotic areas in the skin but no thrombopenia following administration of bismarsen and neoarsphenamine. These studies have been carried out in the hope of obtaining data that would be helpful in elucidating the mechanism causing thrombopenia and purpuric hemorrhages in sensitive, or sensitized, persons after administration of the arsphenamines. We believe, from our experience, that the condition is of much more frequent occurrence than published reports in the literature would indicate. From the time we began these studies on our first observed case (in 1933) until the end of 1938, we have observed and studied 8 patients with typical purpura haemorrhagica following administration of some form of arsphenamine. Seven of these patients have been tested for tolerance to mapharsen, and none has shown any untoward reaction or any evidence of purpura haemorrhagica following therapy with mapharsen.

METHODS AND TECHNIC

Six patients constituted our material and were studied either in the hematologic clinic or in the University of California Hospital. Of these, 5 were women and 1 a man. All were referred from the syphilis clinic because of hemorrhagic phenomena following administration of arsphenamine derivatives. In 4 instances bismarsen was used, and in 2, neoarsphenamine. Blood counts were made with standardized apparatus. The estimations of hemoglobin were made with the Sahli hemoglobinometer (Osgood and Haskins modification [5]). By this method, 13.7 Gm. of hemoglobin equals 100 per cent. The platelet counts were performed according to the Rees and Ecker [6] technic. In these experiments, a count of from 200,000 to 600,000 platelets per cubic millimeter was considered to be within the normal range. Blood counts were made usually in the morning hours, between 9 and 11 a. m. Hematocrit readings were made with Wintrobe [7] pipets. Capillary fragility was estimated by the Dalldorf [8] method, and all readings were based on

4. Stigaard, A.: Care of Thrombopenic Purpura After Arsphenamine Administration Cured by Blood Transfusion, Ugesk. f. læger **99**:138 (Feb. 4) 1937.

5. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, J. Biol. Chem. **57**:107 (Aug.) 1923.

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application of negative pressure for one minute. Our method was to make daily platelet counts after the initial complete blood count made at the first examination of a patient during an attack. After the platelet count had returned to normal or to nearly the normal level, the patient was given a dose of neoarsphenamine (0.1 Gm. or less) intravenously to reproduce the attack. After admin-

TABLE 1.—*Excerpts from Case Histories*

Case, Sex, Age	Type of Arsphenamine Used	Number of Doses and Size of Each Dose	Degree of Reaction and Symptoms	Onset of Purpura Following Reaction	Distribution of Purpuric Lesions	Date Patients First Seen	Type of Syphilis and Complications
1 F 44	Neoarsphenamine Trypharsamide	11 (0.6 Gm.) 1 (0.45 Gm.) 2 (3 Gm.)	Severe; nausea; vomiting and collapse after neoarsphenamine	Few hours	General	March 18, 1936	Cerebrospinal syphilis; tabetic crisis; myocardial weakness (tabetic dementia paralytica)
2 M 66	Neoarsphenamine Arsphenamine Bismarsen	1 (0.9 Gm.) 26 (0.6 Gm.) 4 (0.45 Gm.) 5 (0.2 Gm.) 1 (0.4 Gm.) 3 (0.1 Gm.)	Moderately severe; nausea, headache and chills after bismarsen	Few hours	General	Oct. 8, 1937, 60 hrs. after reaction	Central nervous system syphilis; arteriosclerosis (general)
3 F 45	Neoarsphenamine Mapharsen Bismarsen	18 (0.3 Gm.) 9 (0.15 Gm.) 2 (0.45 Gm.) 2 (0.1 Gm.) 2 (0.2 Gm.) 1 (20 mg.) 12 (0.1 Gm.)	Severe; nausea, vomiting, headache and collapse after neoarsphenamine	24 hrs.	Arms, chest and lower extremities	Nov. 27, 1937, 1 week after reaction	Latent syphilis; aortitis; aortic insufficiency
4 F 48	Neoarsphenamine Bismarsen	1 (0.45 Gm.) 29 (0.2 Gm.)	Severe; nausea, vomiting and chills after bismarsen	24 hrs.	General	Oct. 12, 1938, 24 hrs. after reaction	Latent syphilis; obesity; hypochromic anemia
5 F 30	Neoarsphenamine Bismarsen Mapharsen	1 (0.45 Gm.) 42 (0.2 Gm.) 12 (0.15 Gm.) 1 (20 mg.) 3 (30 mg.)	No general reaction; pain at site of injection; purpura after bismarsen	6 hrs.	Breasts and extremities	Sept. 14, 1938, 24 hrs. after reaction	Secondary syphilis
6 F 42	Neoarsphenamine Mapharsen Bismarsen	12 (?) 1 (0.2 Gm.) 1 (20 mg.) 2 (0.2 Gm.)	Moderate; nausea, vomiting; quantitative reaction to several different arsphenamines	24 hrs.	Ecchymotic areas on arms and lower extremities	May 25, 1937	Latent syphilis

istration, platelet counts were made at intervals of fifteen, thirty, sixty and one hundred and twenty minutes; then daily or less often until the count had returned to normal. This procedure was repeated after administration of mapharsen, beginning with 10 or 20 mg. Usually more than one dose of mapharsen was used in testing the patient's sensitivity to this drug.

PROTOCOLS AND EXPERIMENTAL DATA

CASE 1.—From the excerpt of the case history (table 1) it will be seen that the patient, a woman aged 44, was sensitive to neoarsphenamine.

TABLE 2.—*Platelet Counts and Other Data in Case 1*

Date	Time After Injection	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, %	Hemoglobin, Gm.	Platelets	White Blood Cells per Cu. Mm.	Polymorphonuclears	Filamented Polymorphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Myelocytes	Metamyelocytes	Comment
12/18/36	.....	4.66	86	12.04	300,000	6,000	58	50	8	..	..	28	13	1	..	
12/21/36	15 min.	....	..	.....	320,000	.....	64	58	6	2	..	26	6	..	2	After mapharsen (10 mg.)
	30 min.	....	..	.....	290,000	.....	70	54	16	2	..	18	10			
	45 min.	....	..	.....	330,000	.....	60	54	6	2	..	34	4			
	60 min.	....	..	.....	430,000	.....	56	44	12	2	..	26	16			
12/28/36	.....	4.72	86	12.04	450,000	7,500	60	48	12	4	..	20	16			
1/ 4/37	.....	4.70	86	.....	440,000	7,150	62	40	22	..	..	24	14			
1/11/37	.....	4.68	86	.....	510,000	7,450	52	48	4	2	2	30	14	..	..	Before mapharsen (40 mg.)
	15 min.	....	..	.....	470,000	.....	70	52	18	4	..	14	12	..	..	After
	30 min.	....	..	.....	390,000	.....	86	64	22	..	..	12	2			
	45 min.	....	..	.....	520,000	.....	78	64	14	2	1	13	6			
	60 min.	....	..	.....	540,000	.....	58	38	20	3	..	30	8	1	..	
1/16/37	.....	4.63	86	.....	270,000	7,250	58	50	8	1	1	24	16			
1/21/37	.....	4.59	86	.....	290,000	6,200	50	48	2	2	2	16	30	..	..	Before neoarsphenamine (0.075 Gm.)
	15 min.	....	..	.....	50,000	.....	56	28	28	..	..	36	4	4	..	After
	30 min.	....	..	.....	30,000	.....	94	58	36	..	..	4	2			
	45 min.	....	..	.....	30,000	.....	86	40	46	2	..	12	..			
	60 min.	....	..	.....	20,000	.....	66	32	34	2	1	27	2	..	2	
	5 hrs.	4.45	..	.....	20,000	7,100	94	68	26	..	..	2	..	4	..	
1/22/37	30 hrs.	4.49	86	.....	30,000	7,450	72	64	8	4	..	18	6			Hematocrit:
1/26/37	.....	4.61	86	.....	50,000	7,300	70	66	4	..	..	12	18			Red blood cells, 4,900,000; hemoglobin, 92% = 12.6 Gm.
1/28/37	.....	4.95	86	.....	150,000	7,500	66	50	16	1	..	25	7			Vol. coefficient (packed cells) 43 cc. per 100 cc. blood; normal, 45 to 46 cc.
2/ 3/37	.....	4.98	90	12.3	450,000	9,450	62	46	16	2	..	22	12	2	..	Mean corp. vol. = 87.75 cu. microns; average 87, minimum 80, maximum 94
2/ 9/37	.....	4.94	90	.....	610,000	12,250	68	40	18	6	..	14	12			Mean. corp. hem. = 25.71 micromicrograms; average 29.5, minimum 27, maximum 32
2/16/37	.....	4.93	92	12.6	460,000	8,450	72	54	18	..	..	18	10			Mean corp. hem. concent. 29.3%; average 35%, minimum 33%, maximum 38%
2/23/37	.....	5.50	94	12.8	230,000	7,900	44	34	10	..	..	42	14			Vol. index, 0.953; normal, 0.95 to 1.05
	30 min.	5.54	94	.....	270,000	7,300	70	52	18	2	..	18	10			Color index, 0.938; normal, 0.90 to 1.10

She was next given intravenous injections of mapharsen to test her sensitivity to this arsphenamine derivative. On Dec. 12, 1936, she received 10 mg. of mapharsen. On Jan. 11, 1937, she received a second dose of mapharsen (40 mg.). The platelet counts immediately after the injections and at longer intervals are recorded in table 2. After these injections, she experienced no untoward symptoms, the platelet counts were not decreased significantly and no petechial hemorrhages appeared in the skin or mucous membranes.

On Jan. 21, 1938, the patient was given an intravenous injection of neoarsphenamine (0.075 Gm.) to determine, in a measure, her sensitivity to this drug. While the needle was in the vein and she was still receiving the injection, her face became flushed and a dark reddish hue spread over her face and neck; she complained of a "choking sensation." At the end of the injection the pulse was rapid (130 beats per minute); she became nauseated and vomited; the hands and feet were cold, and a "splitting headache" came on. The acute symptoms gradually subsided. Table 2 shows the rapid drop in the platelet count. On

Fig. 1.—Hemorrhagic blebs appearing twenty-four hours after administration of 0.075 Gm. of neoarsphenamine.

January 22, twenty-four hours after the injection, there were many small, dark red petechiae on the arms, chest and lower extremities. On the upper parts of both arms and over both ankles were ecchymotic areas from 6 to 8 cm. in diameter. In the buccal mucosa on the right there was a hemorrhagic bleb about 2 cm. in diameter, and there were three smaller areas (about 3 mm. in diameter) in the buccal mucosa of the lower lip (fig. 1). On this date she had a slight epistaxis, a small amount of uterine bleeding occurred and the urine showed many red blood cells in each microscopic field.

On February 23 intravenous injections of 40 mg. of mapharsen were started and continued with short periods of rest until December 15. These treatments brought about freedom from her tabetic pains, and the platelet counts (tables 2 and 3) ranged between 160,000 and 300,000 per cubic millimeter. No untoward symptoms and no purpuric or other hemorrhages occurred during her many injections of mapharsen.

Case 2.—A man aged 66, had a reaction from bismarsen on Oct. 7, 1937 (table 1). By October 9 the platelet count had risen to 240,000 per cubic millimeter. On October 12 the platelet count was 360,000. At this time the patient

Table 3.—*Further Platelet Counts and Miscellaneous Data in Case 1*

TABLE 3.—*Further Platelet Counts and Miscellaneous Data in Case 1*

Date	Time After Injection	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, %	Hemoglobin, Gm.	Platelets	White Blood Cells per Cu. Mm.	Polymorphonuclears	Filamented Polymorphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Myelocytes	Metamyelocytes	Comment
3/ 1/37	.....	5.52	94	....	310,000	7,250	58	42	16	4	..	22	14	..	2	
3/ 8/37	.....	5.57	96	13.2	290,000	7,900	60	44	16	2	..	20	18			
3/15/37	.....	5.51	94	12.8	270,000	8,100	69	52	17	1	..	14	16			
3/23/37	.....	5.48	94	....	260,000	8,350	70	62	8	6	..	12	12			
3/29/37	.....	5.66	94	....	200,000	8,600	80	54	26	..	..	14	6			
4/ 5/37	.....	5.61	94	....	220,000	7,400	66	38	28	2	1	12	16	1	2	
4/19/37	.....	5.54	94	....	180,000	9,100	61	45	16	..	1	14	22	..	2	
5/10/37	.....	5.42	96	13.2	220,000	8,800	73	61	12	..	..	22	4	1	..	
5/24/37	.....	5.48	94	12.8	200,000	9,400	58	38	20	4	..	14	24			
6/28/37	.....	5.63	94	....	220,000	7,700	58	43	15	6	..	23	13	..	..	Before mapharsen (40 mg.)
	20 min.	....	..	....	230,000	.....	56	43	13	6	..	28	16	..	..	After
	60 min.	....	..	....	180,000	6,100	52	34	18	4	..	34	10			
7/ 6/37	.....	5.67	94	....	160,000	9,500	58	46	12	..	..	26	16			
	20 min.	....	..	....	190,000	.....	56	46	10	6	..	20	18			
7/12/37	.....	5.80	94	....	170,000	10,050	70	48	22	2	..	19	9	..	..	Before mapharsen (40 mg.)
	30 min.	....	..	....	180,000	.....	70	56	14	3	3	22	2	..	..	After
7/19/37	.....	5.72	96	13.2	240,000	9,000	58	42	16	2	..	18	22	..	..	Before mapharsen (40 mg.)
	30 min.	....	..	....	220,000	9,700	74	60	14	2	..	13	11	..	..	After
7/26/37	.....	5.76	96	....	210,000	7,600	68	50	18	..	..	18	14	..	..	Before mapharsen (40 mg.)
	30 min.	....	..	....	220,000	8,100	66	52	14	1	1	22	18	..	..	After
8/ 2/37	.....	5.70	100	13.8	250,000	8,600	68	52	16	4	..	22	6	..	..	Before mapharsen (40 mg.)
	30 min.	....	..	....	240,000	9,100	56	40	16	2	..	22	20	..	..	After
8/ 9/37	.....	5.59	98	13.4	190,000	7,400	60	40	20	2	..	20	18	..	..	Before mapharsen (40 mg.)
	30 min.	....	..	....	190,000	7,650	50	28	22	6	1	30	13	..	..	After
8/16/37	.....	5.58	98	....	170,000	7,700	78	64	14	..	..	12	10	..	..	Before mapharsen (40 mg.)
	30 min.	....	..	....	190,000	7,950	56	39	17	4	..	25	15	..	..	After
8/23/37	.....	5.54	98	....	210,000	8,150	66	43	23	2	..	16	16			
11/15/37	.....	5.60	100	13.8	290,000	7,100	66	55	11	..	..	26	8	..	..	Before mapharsen (40 mg.)
	15 min.	....	..	....	310,000	.....	52	42	10	1	1	26	20	..	..	After
11/22/37	.....	5.47	100	....	290,000	6,300	38	30	8	2	..	32	28			

TABLE 4.—*Platelet Counts and Other Data in Case 2*

Date	Time After Injection	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, %	Hemoglobin, Gm.	Platelets	White Blood Cells per Cu. Mm.	Polymorphonuclears	Filamented Polymorphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Comment
10/ 8/37	.....	5.58	104	14.25	160,000	14,300	69	61	8	2	1	20	8	
10/ 9/37	.....	5.60	104	.....	240,000	10,200	78	76	2	1	..	13	8	
10/12/37	.....	....	...	.....	360,000	.....	75	73	2	2	..	12	11	Before 6 mg. mapharsen
	15 min.	....	...	.....	300,000	.....	77	65	12	1	1	11	10	After
	30 min.	....	...	.....	350,000	.....	62	56	6	2	..	23	10	
	60 min.	....	...	.....	370,000	.....	62	56	6	..	..	18	20	
	90 min.	....	...	.....	350,000	.....	52	40	12	2	..	32	16	
10/13/37	.....	5.51	104	.....	360,000	9,700	55	46	9	1	..	27	17	
10/16/37	.....	5.46	104	.....	540,000	12,700	66	45	21	4	..	18	12	Before 30 mg. mapharsen
	15 min.	....	...	.....	560,000	.....	75	50	25	2	..	15	..	After
	30 min.	....	...	.....	430,000	.....	70	49	21	..	..	20	10	
	60 min.	....	...	.....	530,000	.....	65	47	18	5	..	15	15	
10/18/37	.....	5.56	104	.....	480,000	11,600	59	45	14	3	..	24	14	
10/21/37	.....	5.68	104	.....	580,000	12,400	62	54	8	4	..	24	10	Before 0.015 Gm. neoarsphenamine
	15 min.	....	...	.....	250,000	11,000	68	60	8	4	..	20	8	After
	30 min.	....	...	.....	80,000	8,500	62	54	8	2	..	32	4	Hematocrit:
	60 min.	....	...	.....	150,000	10,100	76	65	11	2	..	20	2	Packed cell vol., 39; normal, 45-46
	2 hrs.	....	...	.....	170,000	13,900	77	57	20	1	..	20	2	Mean corp. vol., 78; normal, 87
	3 hrs.	....	...	.....	110,000	21,000	82	52	30	2	..	12	4	Mean corp. hgb., 28; normal, 29.5 Mean corp. hgb. concent., 35.9; normal, 35
	7 hrs.	....	...	.....	190,000	14,800	69	58	11	5	..	22	4	Vol. index, 0.899; normal, 0.95-1.05 Color index, 0.949; normal, 0.90-1.10
10/22/37	.....	5.50	102	13.97	100,000	12,600	72	60	12	4	..	19	5	Saturation index, 1.067; normal, 0.87-1.23 Icteric index, 2; normal, 4-7
10/23/37	.....	....	...	.....	130,000	8,000	68	58	10	4	..	22	6	
10/25/37	.....	5.53	102	.....	300,000	7,200	62	52	10	3	..	29	6	—20 cm. pressure, 20-30 petechiae; —15 cm. pressure, 7-9 petechiae
10/26/37	.....	5.58	102	.....	450,000	12,400	70	56	14	2	..	21	7	
10/28/37	.....	5.40	102	.....	300,000	15,100	78	64	14	3	..	16	3	—10 cm. pressure none
11/ 4/37	.....	5.43	102	... .	410,000	15,300	65	55	10	5	..	23	7	—15 cm. pressure, 3 petechiae; —20 cm. pressure, 7 petechiae

was given 6 mg. of mapharsen intravenously in order to determine whether he was sensitive to this drug. We knew that he was sensitive to neoarsphenamine, because he had a history of a severe reaction in 1929 following the taking of 0.45 Gm. of this drug, which had made it necessary for him to enter the University Hospital for two days. After the injection of mapharsen the platelet count fluctuated slightly, but at the end of one and one-half hours it was at about the same level as before the injection (table 4). There were no clinical signs or symptoms of a reaction.

On October 21 the Dalldorf capillary fragility test showed:

—25 cm. pressure	8 to 10 petechiae
—20 cm. pressure	3 to 5 petechiae
—15 cm. pressure	no petechiae

Fig. 2.—Purpuric lesions which appeared two hours after injection of 0.015 Gm. of neoarsphenamine.

These tests were done at 9 a. m., and at 9:30 a. m. 0.015 Gm. of neoarsphenamine was administered intravenously. Immediately afterward, the patient complained of nausea and became cyanotic; the pulse was rapid, and he felt faint. The blood pressure dropped from 120 mm. of mercury systolic and 80 diastolic to 85 systolic and 60 diastolic. Thirty minutes after the injection the platelet count was 80,000 per cubic millimeter. At this time the Dalldorf capillary fragility test showed:

—15 cm. pressure	a shower of petechiae
—10 cm. pressure	20 to 25 petechiae

Two hours after the injection, purpuric spots appeared on the upper anterior surface of the chest, on the arms and below the knees (fig. 2). At this time the patient had a chill, for which 1 cc. of epinephrine hydrochloride (1:1,000) was administered subcutaneously. The platelet count rose to 170,000 per cubic millimeter. The patient was transferred from the clinic to the hospital. Seven hours after the injection and just after a hot tub bath, the platelet count was 190,000

per cubic millimeter. On October 22, twenty-four hours after the injection, the Dalldorf capillary fragility test showed:

— 15 cm. pressure..... a shower of petechiae
— 10 cm. pressure..... 30 petechiae

On October 23, the test showed:

— 20 cm. pressure..... 40 to 50 petechiae
— 15 cm. pressure..... 30 to 35 petechiae
— 10 cm. pressure..... 12 to 20 petechiae

On October 25, the platelet count was 300,000, and the test showed:

— 20 cm. pressure..... 20 to 30 petechiae
— 10 cm. pressure..... 7 to 9 petechiae

On November 4, the platelet count was 410,000, and the test showed:

— 20 cm. pressure..... 7 petechiae
— 15 cm. pressure..... 3 petechiae
— 10 cm. pressure..... no petechiae noted

Case 3.—On Nov. 29, 1937, a woman aged 45 who was known to be sensitive to neoarsphenamine (table 1) was tested with 20 mg. of mapharsen administered intravenously. The platelet count rose immediately after this injection (table 5); no untoward symptoms occurred. On December 3 she received 0.1 Gm. of neoarsphenamine intravenously. While still receiving the injection, she began to complain of nausea. As soon as the injection was finished, vomiting occurred, the pulse became rapid and feeble, the hands and feet were cold and a severe headache came on. Two hours after the injection, petechiae appeared on the upper parts of both arms and on both lower extremities below the knees. At the end of thirty minutes after the injection, the platelet count was 80,000 per cubic millimeter; sixty minutes after the injection, the count was 130,000; one hundred and twenty minutes after the injection, the count was 190,000. On the following day the platelet count was 70,000 per cubic millimeter. This was the first time we had observed a temporary rise in the platelet count following administration of neoarsphenamine to a patient known to be sensitive to this drug and to have previously exhibited purpura haemorrhagica following its intravenous use.

Case 4.—On Oct. 10, 1938, after an intramuscular injection of 0.2 Gm. of bismarsen, the patient, a woman aged 48, had a severe reaction, the thrombocytes dropping as low as 50,000 per cubic millimeter. By October 17 the platelet count had risen to 310,000. In order to test her sensitivity, we gave her on this date 20 mg. of mapharsen intravenously. The platelet count was not lowered by this drug (table 6), and no reaction of any type was noted after the injection.

When she was first seen in the hematologic clinic we noted the presence of hypochromic anemia, and she was given intramuscular injections of concentrated liver extract (Lilly) with ferrous sulfate (0.23 Gm., four doses daily). In addition to its possible effect on the hemopoietic system, we desired to ascertain whether liver extract exercises an ameliorating effect on the toxic reaction occurring after administration of the arsphenamine to a patient sensitive to at least one of these preparations, the sulfarsphenamine or bismarsen. On both November 22 and November 29 she was tested further with 40 mg. of mapharsen. No significant change in the platelet counts occurred, and she showed no evidence of reaction. On December 14, 0.1 Gm. of neoarsphenamine was administered intravenously. The platelet count dropped slightly (table 6), but there were

TABLE 5.—*Platelet Counts and Other Data in Case 3*

Date	Time After Injection	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, %	Hemoglobin, Gm.	Platelets	White Blood Cells per Cu. Mm.	Polymorphonuclears	Filamented Polymorphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Metamyelocytes	Comment
11/27/37	.....	5.60	104	14.25	200,000	10,300	68	54	14	6	..	14	12	..	7 days after neoarsphenamine (0.2 Gm.) and purpura haemorrhagica
11/29/37	15 min.	....	...	.....	210,000	11,400	80	75	5	..	..	16	4	..	Before mapharsen (20 mg.)
	30 min.	....	...	.....	280,000	9,600	66	50	16	1	1	30	2		
	60 min.	....	...	.....	260,000	10,300	79	63	16	3	..	12	6		
	120 min.	....	...	.....	310,000	.....	52	30	20	3	1	40	4		
12/ 3/37	.....	5.41	104	14.25	270,000	8,500	82	57	25	4	..	9	4	1	Before neoarsphenamine (0.1 Gm.)
	15 min.	....	...	.....	160,000	6,200	78	57	21	2	..	15	3	2	An occasional very large platelet; all others very small in counting chamber
	30 min.	....	...	.....	80,000	7,600	90	68	22	2	..	8	..		
	60 min.	....	...	.....	130,000	8,100	84	74	10	1	..	13	2		
	120 min.	....	...	.....	190,000	9,150	76	53	23	5	..	19	..	*	
12/ 4/37	.....	....	...	.....	70,000	11,200	72	64	8	6	..	18	4		
12/ 6/37	.....	5.44	104	.....	140,000	9,800	69	60	9	2	..	21	8		
12/ 7/37	.....	5.77	104	.....	240,000	11,400	58	40	18	2	..	32	8		
12/ 8/37	.....	5.70	104	.....	270,000	10,300	62	50	12	4	..	22	12		
12/ 9/37	.....	5.76	104	.....	280,000	9,100	70	56	14	..	..	26	4		
12/10/37	.....	5.80	104	.....	380,000	12,900	72	64	8	3	..	32	3		
12/11/37	.....	6.01	104	.....	370,000	8,800	66	50	16	2	..	18	14		
12/16/37	.....	6.03	104	.....	580,000	9,700	70	56	14	3	..	19	8		
12/23/37	.....	5.97	104	.....	510,000	10,300	62	50	12	5	..	29	4		
12/29/37	.....	5.84	104	.....	480,000	12,200	82	64	22	..	..	16	2		
1/ 3/38	.....	5.80	104	.....	400,000	9,600	72	60	12	4	..	21	3		

TABLE 6.—*Platelet Counts and Other Data in Case 4*

Date	Time After Injection	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, %	Hemoglobin, Gm.	Platelets	White Blood Cells per Cu. Mm.	Polymorphonuclears	Filamented Polymorphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Comment
10/11/38	.....	5.50	66	9.0	70,000	8,900	60	49	11	2	..	20	18	
					70,000	.....	74	62	12	2	..	12	12	
10/12/38	.....	5.30	66	....	50,000	8,100	70	52	18	2	..	16	12	
10/13/38	.....	4.97	64	8.77	100,000	9,400	69	60	9	1	1	17	12	
10/14/38	.....	4.80	64	....	130,000	9,800	65	52	13	2	2	18	13	
10/15/38	.....	4.62	62	8.49	140,000	10,000	62	52	10	1	1	25	11	
10/17/38	.....	4.71	64	8.77	310,000	11,000	69	59	10	3	1	15	12	Before 20 mg. mapharsen
	15 min.	....	..	....	330,000	13,600	72	63	9	2	..	16	10	After
	30 min.	....	..	....	330,000	12,900	70	48	22	3	..	20	7	
	60 min.	....	..	....	350,000	12,600	73	55	18	2	..	11	14	
	90 min.	....	..	....	310,000	11,900	69	51	18	1	..	20	10	
10/18/38	.....	4.68	62	8.49	320,000	11,800	66	53	13	..	1	21	12	
10/20/38	.....	4.60	62	....	340,000	13,400	66	52	14	2	..	18	14	Lilly's sol. liver ext. conc. 3 cc. intramuscularly twice per week
10/22/38	.....	4.57	62	....	590,000	13,800	72	60	12	1	1	14	12	
10/25/38	.....	4.63	60	8.22	570,000	10,050	70	64	6	2	2	18	8	
10/27/38	.....	4.60	60	....	410,000	11,800	70	62	8	2	..	12	16	
11/14/38	.....	4.80	58	7.95	590,000	14,000	65	55	10	2	..	17	16	
11/18/38	.....	4.87	64	8.77	690,000	14,300	..	..	..	..	..	..	..	
11/22/38	.....	4.90	62	8.49	680,000	15,700	66	52	14	3	1	20	10	Before 40 mg. mapharsen
	15 min.	....	..	....	880,000	15,400	64	50	14	1	..	22	12	After
	30 min.	....	..	....	760,000	12,800	69	54	15	2	..	18	11	
	60 min.	....	..	....	680,000	14,900	70	50	20	..	..	10	20	
	2 hrs.	....	..	....	670,000	15,200	71	60	11	3	1	10	15	
11/29/38	.....	5.10	80	10.96	430,000	13,100	67	65	2	3	..	16	14	Before 40 mg. mapharsen
	15 min.	....	..	....	460,000	14,300	66	58	8	2	..	18	14	After
	30 min.	....	..	....	470,000	13,800	..	..	..	..	..	..	..	
	60 min.	....	..	....	450,000	13,700	70	56	14	3	1	18	8	
12/ 5/38	.....	5.04	76	10.41	710,000	18,300	74	60	14	..	..	12	14	
12/14/38	.....	5.02	70	9.59	540,000	9,300	80	76	4	1	1	10	8	Before 0.1 Gm. neoarsphenamine
	15 min.	....	..	....	510,000	9,600	79	68	11	1	..	12	8	After
	30 min.	....	..	....	510,000	8,600	84	74	10	..	..	12	4	
	60 min.	....	..	....	480,000	12,100	78	69	9	..	..	16	6	
	90 min.	....	..	....	490,000	11,300	83	77	6	1	..	10	6	

TABLE 7.—*Further Platelet Counts and Miscellaneous Data in Case 4*

TABLE 7.—*Further Platelet Counts and Miscellaneous Data in Case 4*

Date	Time After Injection	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, %	Hemoglobin, Gm.	Platelets	White Blood Cells per Cu. Mm.	Polymorphonuclears	Filamented Polymorphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Myelocytes	Metamyelocytes	Comment
12/21/38	.....	5.05	68	9.32	420,000	10,700	74	59	15	1	..	15	10	..	..	Before 0.1 Gm. neoarsphenamine
	15 min.	....	..	....	490,000	11,800	69	63	6	1	..	18	12	..	..	After
	30 min.	....	..	....	620,000	11,300	72	67	5	1	..	16	11			
	60 min.	....	..	....	590,000	12,100	72	66	6	..	..	18	10			
	90 min.	....	..	....	500,000	11,900	72	68	4	1	..	15	12			
12/22/38	.....	....	..	....	480,000	11,800	73	59	14	1	..	14	12			
12/30/38	.....	5.16	66	9.04	570,000	9,200	72	64	8	4	..	14	10	..	..	Before 0.1 Gm. bismarsen
	15 min.	....	..	....	510,000	7,800	72	63	9	2	1	14	11	..	..	After
	30 min.	....	..	....	460,000	16,300	76	63	13	..	..	15	7	1	..	
	60 min.	....	..	....	300,000	12,100	82	52	30	2	..	10	6			
	90 min.	....	..	....	210,000	9,300	87	57	30	..	..	8	5	..	..	Epinephrine, 1 cc. (1:1,000)
	2 hrs.	....	..	....	320,000	9,100	85	50	35	2	1	5	7			
	3 hrs.	....	..	....	170,000	8,400	84	51	33	2	1	6	7			
12/31/38	a.m.	5.14	64	8.77	60,000	11,500	70	54	16	1	1	12	16			
	p.m.	....	..	....	80,000	12,100	78	64	14	3	..	10	9			
1/ 3/39	.....	4.83	60	8.22	110,000	15,750	74	62	12	4	1	12	9			
1/ 4/39	.....	4.88	60	....	160,000	19,100	70	60	10	4	2	12	12			
1/ 5/39	.....	4.81	60	....	320,000	17,300	70	63	7	3	4	9	14			
2/20/39	.....	5.41	62	8.49	560,000	13,400	66	65	1	2	..	18	14	..	..	Before 0.1 Gm. sulfarsphenamine
	15 min.	....	..	....	30,000	12,900	61	12	49	..	..	28	8	..	3	After
	60 min.	....	..	....	20,000	14,700	92	38	54	..	..	6	2			
	3 hrs.	....	..	....	25,000	15,100	84	29	55	1	..	10	9	..	1	
	8 hrs.	5.54	62	....	50,000	16,300	88	44	44	..	..	8	4			
2/21/39	.....	4.72	56	7.67	80,000	14,000	88	36	52	..	..	8	4			
2/22/39	a.m.	4.74	54	7.40	80,000	10,300	82	62	20	..	..	7	11			
	p.m.	4.70	54	....	90,000	11,400	83	66	20	..	..	6	7			
2/23/39	a.m.	4.38	50	6.85	120,000	13,000	88	67	21	..	..	7	5	..	..	Hematocrit:
	p.m.	4.31	50	....	100,000	13,600	82	62	20	..	..	7	11	..	..	Packed cell volume, 33; normal average, 45-46
2/24/39	a.m.	4.29	50	....	140,000	9,300	79	60	19	1	..	9	11	..	..	Mean corpuscular volume, 73.3; normal, 87
	p.m.	4.33	50	....	190,000	10,500	82	68	14	3	..	10	5	..	..	Mean corpuscular hemoglobin, 1.83; normal, 29.5
2/25/39	.....	4.41	52	7.12	240,000	13,600	82	72	10	2	..	13	3	..	..	Mean corpuscular hemoglobin conc. 24.9; normal, 35
2/28/39	.....	4.30	54	7.4	480,000	21,300	72	63	9	3	..	16	9	..	..	Volume index, 0.84; normal, 0.95-1.05
3/ 1/39	.....	4.33	56	7.67	440,000	22,700	74	54	20	4	..	12	10	..	..	Color index, 0.62; normal, 0.90-1.10
3/ 2/39	.....	4.41	56	....	390,000	18,900	72	59	13	..	..	18	10	..	..	Saturation index, 0.74; normal, 0.87-1.23
3/11/39	.....	4.50	60	8.22	410,000	12,300	70	62	8	1	..	21	8			

no untoward symptoms following the injection. On December 21 a second intravenous injection of neoarsphenamine (0.1 Gm.) was given. The platelet count gradually rose after the injection. On the next day the number of platelets was still above the level of the count made just before the neoarsphenamine was administered (table 7). No reaction of any sort was observed from this second dose. We decided to test her sensitivity to bismarsen; accordingly, on December 30, she received an intramuscular injection of 0.1 Gm. of bismarsen in the left buttock. The platelet count before the injection was 570,000 per cubic millimeter; ninety minutes after the injection it dropped to 210,000. The patient became nauseated and was pale; the pulse was rapid and weak, and the hands and feet were cold immediately after the injection. Ninety minutes after the bimarsen was given, a chill came on; and, as the pulse was rapid and weak, she was given 1 cc. of epinephrine hydrochloride (1:1,000) subcutaneously. The platelet count rose immediately and two hours after the injection it was 320,000 per cubic millimeter. On the following day, December 31, the platelet count was 60,000, and a purpuric eruption had appeared on the anterior surface of the chest, the abdomen, both arms and the lower extremities. On Feb. 20, 1939, fifty-two days after the injection of bimarsen, the patient was tested to determine her sensitivity to sulfarsphenamine. After a preliminary intramuscular injection of 3 cc. of Lilly's concentrated liver extract, 0.1 Gm. of sulfarsphenamine was slowly injected intravenously. When the last portion of the solution was entering the vein the patient became cyanotic, said that her head felt very peculiar and without further warning fell forward, collapsing in her chair. Because of her obesity she had been allowed to sit in a chair while receiving the injection. She was stretched ont immediately on the floor, and artificial respiration was employed, as her body had become rigid and respirations had ceased. One cubic centimeter of epinephrine hydrochloride (1:1,000 solution) was administered subcutaneously. The pulse was feeble but slow. Under artificial respiration she began to breathe again, and after two or three minutes the rigidity of her body disappeared and she became conscious, asking what had happened. A second dose of 1 cc. of epinephrine hydrochloride (1:1,000 solution) was given. Twenty minutes after the injection the platelet count was 30,000 per cubic millimeter, and purpuric areas from 1 to 3 mm. in diameter began to appear on the neck, the upper anterior surface of the chest and the arms. She began to expectorate blood-tinged mucus, and her lungs became filled with coarse, moist rales. She was admitted at once to the University of California Hospital and placed in an oxygen tent, as it was evident that pulmonary edema had supervened. The development of mild bronchopneumonia necessitated a stay of eleven days in the hospital, but she made an uneventful recovery.

Case 5.—The patient was a Negress aged 30. On Sept. 13, 1938, about three and one-half hours after the fifty-fourth intramuscular injection of bismarsen in a dose of 0.2 Gm., she began to expectorate blood-tinged saliva. No obvious reaction to the injection of bismarsen occurred except pain at the site of injection. She expectorated considerable blood during the night following her treatment, and on the next day, September 14, there were many small petechiae on her chest and extremities (fig. 3). She reported to the syphilis clinic on this date and was admitted to the hospital, since by this time bleeding from the gingival margins had appeared. A few hours after she entered the hospital, the blood pressure in millimeters of mercury dropped from 130 systolic and 80 diastolic to 100 systolic and 60 diastolic. At entry, the bleeding time (Duke) was fifteen minutes; the blood clot showed no retraction after forty-eight hours. At this time the platelet count was 30,000 per cubic millimeter (table 8). After entry, the patient stated that for ten years she had been addicted to the use of morphine. Between

September 16 and September 19 (the date of discharge from the hospital), she received one hypodermic injection of morphine sulfate of 0.01 Gm. and thirteen hypodermic injections of morphine sulfate of 0.03 Gm. each.

A biopsy of the sternal marrow was performed by Dr. Stacy R. Mettier on September 16. Bleeding from the gums had ceased by September 15. On September 17 the patient received an intravenous injection of 10 mg. of mapharsen. By September 19, the platelet count had risen to 300,000 per cubic millimeter; the patient felt well and, at her request, was discharged from the hospital.

She returned to the hematologic clinic on October 4 and was given an intravenous injection of 15 mg. of mapharsen (table 8). On October 18 she received 0.1 Gm. of neoarsphenamine intravenously (see table 8 for results). While in the hospital, she had been tested for sensitivity to mapharsen, and she was tested again shortly after discharge. This last injection was to ascertain whether she was sensitive to neoarsphenamine. There were no untoward subjective symptoms of

Fig. 3.—Closely packed petechiae on the arm twenty-four hours after administration of bismarsen.

any kind during or after this injection of neoarsphenamine, but the number of platelets decreased rapidly, and four hours after the injection the bleeding time was thirty-five minutes. The blood clot showed no retraction after twenty-four hours.

CASE 6.—After a series of twelve intravenous injections in Chicago in 1929, a woman aged 42 could not tolerate further treatment with neoarsphenamine without onset of nausea, vomiting and malaise. The drug injected in 1929 was presumably neoarsphenamine, but we have only the patient's opinion concerning its identity. During October 1935, after intravenous injection of 20 mg. of mapharsen, nausea and vomiting occurred. Between October 1935 and July 1936, she received twenty-six intramuscular injections of bismarsen (0.2 Gm. each), with no apparent reactions and no hemorrhagic phenomena. On April 30, 1937, after intravenous injection of 0.2 Gm., she immediately had symptoms of nausea and vomiting. During May 1937 she received two intramuscular injections, each of 0.2 Gm. of bismarsen. After each injection large ecchymotic areas appeared

TABLE 8.—*Platelet Counts and Other Data in Case 5*

Date	Time After Injection	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, %	Hemoglobin, Gm.	Platelets	White Blood Cells per Cu. Mm.	Polymorphonuclears	Filamented Polymorphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Comment
9/14/38	Noon	4.70	96	13.15	30,000	12,200	50	48	2	1	1	30	18	Count during first reaction to 0.2 Gm. bismarsen
	6 p.m.	....	..	.....	30,000	12,300	73	70	3	..	..	19	..	9/16/38, sternal biopsy
	8 p.m.	....	..	.....	50,000	12,400	81	71	10	1	1	11	6	Myeloblasts, 6
9/15/38	8 a.m.	4.76	96	.. ..	80,000	12,400	76	66	10	4	..	16	4	Myelocytes: neutrophils 13, eosinophils 2
	12 noon	....	..	.. ..	70,000	12,600	68	58	10	1	..	20	11	Metamyelocytes: neutrophils 17, eosinophils 2
	4 p.m.	....	..	.....	80,000	11,800	61	50	11	..	..	27	12	Polymorphonuclears: neutrophils 24, eosinophil 1
	6 p.m.	....	..	.....	100,000	9,900	54	42	12	..	..	30	16	Lymphocytes, 7
9/16/38	8 a.m.	4.68	96	.....	70,000	8,700	74	66	8	2	..	18	6	Megakaryocytes, 0
	12 noon	....	..	.. ..	90,000	8,900	75	69	6	4	..	17	4	Megaloblasts, 6
	5 p.m.	....	..	.....	100,000	8,600	68	60	8	2	2	18	10	Normoblasts, 23
9/17/38	8 a.m.	4.74	96	.....	200,000	7,400	76	64	12	1	1	14	8	
					240,000	8,300	75	67	8	1	1	13	10	Before 10 mg. mapharsen
	2 hrs.	....	..	.....	260,000	8,850	73	71	2	1	1	13	12	After
	4 hrs.	....	..	.....	270,000	8,350	75	70	5	2	..	15	8	
	6 hrs.	....	..	.....	250,000	8,600	73	70	3	1	1	15	10	
9/18/38	8 a.m.	4.78	..	.....	290,000	9,100	62	58	4	1	..	21	16	
	5 p.m.	....	..	.....	300,000	9,300	66	60	6	2	..	21	11	
9/19/38	.....	4.80	96	.....	340,000	11,200	70	60	10	3	..	19	8	
10/ 4/38	.....	4.60	90	12.33	410,000	9,100	56	52	4	5	..	30	9	Before 15 mg. mapharsen
	15 min.	....	..	.....	390,000	9,900	60	52	8	1	..	27	12	After
	30 min.	....	..	.....	420,000	9,700	58	48	10	..	..	27	15	
	60 min.	....	..	.....	400,000	9,900	60	56	4	6	..	24	10	
	2 hrs.	....	..	.....	400,000	9,700	62	52	10	4	1	23	10	
10/18/38	.....	4.82	88	12.06	380,000	9,800	58	48	10	1	1	33	7	Before 0.1 Gm. neoarsphenamine
	15 min.	....	..	.....	200,000	8,900	66	55	11	2	1	27	4	After
	30 min.	....	..	.....	110,000	8,500	80	68	12	1	..	15	4	
	60 min.	....	..	.. ..	65,000	8,600	72	60	12	2	..	18	8	Hematocrit:
	1¾ hrs.	....	..	.....	48,000	8,700	77	65	12	4	1	12	6	Packed cell volume, 40; normal average, 45-46
														Mean corpuscular volume, 78.5; normal, 87
	4 hrs.	....	..	.....	40,000	8,800	74	58	16	2	1	17	6	Mean corpuscular hemoglobin, 24.7; normal, 29.5
														Mean corpuscular hemoglobin concentration, 31.5; normal, 35
10/19/38	.....	4.72	..	.....	100,000	9,100	54	48	6	..	..	28	18	Volume index, 0.90; normal, 0.95-1.05
														Color index, 0.84; normal, 0.90-1.10
10/20/38	....	4.80	90	12.33	270,000	8,800	50	42	8	6	..	37	7	Saturation index, 0.93; normal, 0.87-1.23
														Icteric index, 5; normal, 4-7
10/25/38	.....	4.71	88	12.03	340,000	9,000	50	44	6	1	1	36	12	

10/25/38	.....	4.71	88	12.03	340,000	9,000	50	44	6	1	1	36	12	

TABLE 9.—*Platelet Counts and Other Data in Case 6*

Date	Time After Injection	Red Blood Cells, Millions per Cu. Mm.	Hemoglobin, %	Hemoglobin, Gm.	Platelets	White Blood Cells per Cu. Mm.	Polymorphonuclears	Filamented Polymorphonuclears	Nonfilamented Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Monocytes	Comment
5/25/37	.....	5.97	84	11.51	100,000	11,750	46	36	10	1	1	30	22	Before 0.1 Gm. neoarsphenamine
	15 min.	....	..	.....	240,000	. ....	66	59	7	2	1	25	6	After
	30 min.	....	..	.....	140,000	.....	65	54	11	3	..	28	4	
	45 min.	....	..	.....	120,000	.....	71	61	10	..	..	23	6	
	60 min.	....	..	.....	120,000	.....	67	60	7	3	..	23	7	
5/26/37	.....	5.91	84	.....	100,000	11,600	54	36	18	..	..	32	14	
5/27/37	.....	5.87	84	.....	120,000	10,900	56	35	21	2	1	32	9	
5/28/37	.....	5.93	84	.....	150,000	9,600	40	24	16	1	..	43	16	

on the arms and lower extremities. On May 25 when this patient presented herself for study of the type of reactions she exhibited after treatment with the arsphenamines, she was given a test dose of 0.1 Gm. of neoarsphenamine intravenously. No untoward symptoms followed this injection. The platelet count rose immediately after the injection (table 9). In twenty-four hours it had returned to the level of the count before the injection (100,000 per cubic millimeter). No late toxic symptoms appeared, but twenty-four hours after administration of 0.1 Gm. of neoarsphenamine, two ecchymotic areas about 3 cm. in diameter appeared at the site of the injection into the vein, and over the internal condyle of the right knee there was an ecchymotic area 5 by 4 cm. Results of the Dalldorf capillary fragility test were as follows.

Before injection of neoarsphenamine April 30:

—25 cm. pressure	4 petechiae.
—20 cm. pressure	4 petechiae.

Two hours after injection:

—25 cm. pressure	4 petechiae.
—15 cm. pressure	3 petechiae.

Twenty-four hours after injection:

—30 cm. pressure	6 petechiae.
—25 cm. pressure	3 petechiae.
—20 cm. pressure	3 petechiae.
—15 cm. pressure	no petechiae.

ANALYSIS OF DATA AND COMMENT

Analysis of Case 1.—The data show that the patient had become very sensitive to neoarsphenamine after eleven injections of 0.6 Gm. each and one of 0.45 Gm. Later, when she was given an intravenous injection of neoarsphenamine of as small an amount as 0.075 Gm. she showed an immediate reaction characterized by circulatory collapse and stasis indicative of shock. The rapidity with which the symptoms appeared after the injection was begun suggested a toxic action on the vasomotor centers; in fact, it appeared as if the stage had been previously set for a reaction to occur, so prompt was the response. In contrast to this reaction was the absence of any observable reaction following intravenous injections of mapharsen, of which the patient received some twenty-three while under our observation, the doses varying from 20 to 40 mg. She also received six intravenous injections of tryparsamide, 0.6 Gm. each, without reaction; but after the seventh injection (of 0.6 Gm.) a reaction occurred in the form of pains in the extremities, edema of the lower extremities, nausea and vomiting. Unfortunately she was not sent to us at this time for study, and we do not know whether the platelet count had decreased. No purpuric manifestations appeared.

Analysis of Case 2.—Analysis of the patient's reaction to bismarsen shows that it came on within a few hours after the injection and was characterized by nausea, headache and chills. The longer period in

the development of his reaction may have been due to the fact that this drug was administered intramuscularly. It should be noted that he was very sensitive to neoarsphenamine also. After injection of 0.015 Gm. intravenously, he exhibited mild but prompt symptoms of shock. The results of the Dalldorf capillary fragility test were normal before the injection of neoarsphenamine but paralleled the immediate rapid drop in the platelet count and the subsequent rise following the twenty-four hour interval after injection. A significant feature in connection with these data is the considerable increase in the platelet counts following the subcutaneous injection of 1 cc. of 1:1,000 epinephrine and the hot bath given seven hours after the administration of 0.015 Gm. of neoarsphenamine. It seems apparent that these measures increased the circulatory tone by contracting the capillary bed and restored to the general circulation platelets that were temporarily out of circulation. It seems probable that in instances of this type the dilated capillary bed allows diffusion of blood into the skin, resulting directly in the small hemorrhages constituting the purpura haemorrhagica. The greater portion of platelets may pass out from the arterial circulation into the capillaries but are unable to prevent diffusion of blood from the capillaries.

Analysis of Case 3.—The patient in this case was the third of this series to exhibit phenomena of shock following administration of a test dose of neoarsphenamine. She was a "cardiac invalid" and therefore was not a fit subject for reproducing neoarsphenamine reactions. For this reason our experimental procedures with her were limited. She did not show any reaction to 20 mg. of mapharsen given intravenously. After the test dose of neoarsphenamine (0.1 Gm.) the platelet count dropped rapidly, but one hour after the injection the platelet count began to rise, and two hours after the injection the count was 190,000 per cubic millimeter (more than double the number of platelets fifteen minutes after the injection). This was the only time we have noted a rise of platelets following reaction from an arsenical once the count had begun to fall, except as has been noted (when epinephrine had been administered or other procedures used).

Analysis of Case 4.—Two interesting and important features deserve special mention in the analysis of our data on case 4. The patient was very sensitive to bismarsen, having received some twenty-nine injections before we began our studies. She did not appear to be sensitive to neoarsphenamine. Her history indicated that she had received only one previous dose (0.45 Gm. given intravenously), after which there had been no reaction. We gave her two intravenous injections of neoarsphenamine of 0.1 Gm. each. There was no reaction and no significant drop in the platelet count. The absence of a reaction and of any untoward symptoms following administration of neoarsphenamine might

be ascribed to the protective action of her previous intramuscular injections of liver extract. If this were true, we should expect some degree of similar protection against the toxic systemic effects of bismarsen and sulfarsphenamine. Her reactions to these two substances were strong evidence against any protective value of parenterally administered liver extract in ameliorating the toxic effects of the arsphenamines. In respect to the platelet counts after injection of sulfarsphenamine, table 5 B shows that no rise occurred after two subcutaneous injections of 1 cc. of epinephrine hydrochloride (1:1,000 solution), such as we noted in case 2. An explanation that seems quite probable is that the patient's tissues were unable to absorb the epinephrine owing to extreme shock, with the accompanying feeble circulation and capillary stasis.

Analysis of Case 5.—In the data on case 5, it is important to note that this patient had received some fifty-three injections of bismarsen (0.2 Gm. each) before purpura followed its use. When she did finally become sensitized to bismarsen, she failed to have the severe constitutional symptoms usually seen. The same facts apply to her sensitivity to neoarsphenamine. We believe she had systemic reactions as well as thrombopenic purpura, but the reaction was probably modified by her addiction to a drug (morphine). The fall of blood pressure occurring the first two hours after hospitalization accompanied by a platelet count of 30,000 per cubic millimeter suggests a constitutional reaction.

A sternal biopsy (button type) was performed while the patient was in the hospital at the time that her platelet counts were from 70,000 to 90,000 per cubic millimeter. A few megakaryocytes were observed on the film, but in a differential cell count of 500 cells none were found. Both the erythroid and the myeloid elements of the marrow apparently had been stimulated. We do not have any explanation for this finding, but one of us (E.H.F.) has observed the same type of apparent marrow stimulation associated with thrombopenic purpura following ingestion of sedormid (allylisopropylacetylcarbamide).

Analysis of Case 6.—Our main reason for including the data on the patient in this case was to call attention to the fact that after administration of the arsenicals hemorrhagic phenomena may occur which are quite distinct from thrombopenic purpura and are due to a different mechanism from that of thrombopenic purpura. For example, this patient exhibited a toxic reaction to neoarsphenamine, bismarsen and mapharsen, but when the dose of neoarsphenamine was cut down to 0.1 Gm. (given intravenously) she showed no constitutional reaction, yet hemorrhages into the tissues, evidenced by large ecchymotic areas, took place. When we first examined the patient, her platelet count was below normal; however, after administration of 0.1 Gm. of neoarsphenamine, the count was not depressed further, but rose and did not

return to the original level for twenty-four hours (table 7). No petechial lesions were noted during the experiment. The results of the Dalldorf capillary fragility test showed decreased capillary fragility, indicating that were one to consider increased capillary permeability and fragility responsible for the areas of ecchymosis, the toxic action of the arsphenamines on her capillaries must have been local instead of general, for the capillaries other than those in the area of hemorrhage appeared to be normally resistant. This type of hemorrhagic reaction to the arsphenamines obviously requires further study.

SUMMARY

Data are presented on 5 patients who had purpura haemorrhagica following treatment with arsphenamine derivatives. In 2 the condition followed administration of neoarsphenamine; in 3 it occurred after bismarsen was given. A sixth case is described in which hemorrhagic phenomena occurred after therapy with bismarsen and neoarsphenamine, without marked decrease of platelets and without purpuric lesions.

Each of the 5 patients who exhibited purpura haemorrhagica after administration of the arsphenamines was tested for sensitivity to mapharsen. In no instance was there any constitutional reaction, nor were any untoward symptoms observed. In none of these 5 patients did the intravenous injection of mapharsen cause marked depression of the platelet count, petechiae of the skin or other evidences of capillary hemorrhage.

Our observations and studies in cases 1 to 5, made after test doses of the arsphenamines to which these patients were sensitive, showed that varying degrees of shock occurred, suggesting that the reaction was an allergic phenomenon rather than due to the toxic effects of oxidation or to a changed chemical form of the drug injected. The prompt loss of circulatory tone accompanying the reaction appears to be a vasomotor effect, with loss of capillary tonus, dilatation of the capillary bed and a rapid loss of platelets from the general circulation. It is difficult to believe that such enormous numbers of platelets could be destroyed within fifteen minutes after the drug is injected. The fact that a great number of platelets can be returned promptly into the general circulation by injection of 1 cc. of epinephrine hydrochloride (1:1,000 solution), and the rapid rise of the platelet count within twenty-four to forty-eight hours after the reaction are evidence against the assumption of widespread destruction of the platelets.

The blood cells other than the platelets showed little if any change during these experiments. There appeared to be a tendency to an increase of the polymorphonuclear cells following a reaction, particularly a severe reaction. This may well be a phenomenon similar to the leukocytosis associated with protein shock.

DEGENERATIVE LESIONS IN THE CERVICAL PORTION OF THE SPINE

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The current concept that the hypertrophic variety of spondylitis (spondylitis osteoarthritica) is not an arthritis but a spondylosis arising as a reaction to changes primary in the intervertebral disks is based on the views promulgated by Schmorl and his followers.[1] The intervertebral disks, through the effect of age and of continuous functional stress, pass through stages of fibrillation, dehydration, fissuring and "brown degeneration." Defects in the cartilage plates, which may be congenital, traumatic or infectious in origin, permit extrusion of disk material into the vertebral bodies and penetration of vessels from the spongiosa into the normally avascular intervertebral disks, which may become calcified or ossified. The thinning of the disks and the loss of their normal buffer effect are attended by sclerosis of the adjacent vertebral borders and by marginal proliferation which may proceed to bony ankylosis. This progressive series of events has been duplicated experimentally.[2]

The lower part of the cervical and the lumbar region of the spine demonstrate these degenerative changes most frequently, probably because of the greater susceptibility of these regions to functional trauma. The attention of most pathologists, clinicians and roentgenologists who have written on this subject has been focused on the lumbar region, especially in its relation to pain low in the back and to the sciatic syndrome. Degeneration of the posterior part of the intervertebral disk and increased lordosis of the lumbar portion of the spine have been stressed as factors in the narrowing of the intervertebral foramens associated with direct impingement on the spinal nerves, while the contact of the facet margins against the pedicle above, or the lamina below, after "subluxation" at the zygapophysial joint, has been suggested as

From the Daniel Baugh Institute of Anatomy, Jefferson Medical College.

1. (*a*) Schmorl, G., and Junghanns, H.: Die gesunde und kranke Wirbelsaüle im Roentgenbild, Leipzig, George Thieme, 1932. (*b*) Junghanns, H.: Die Pathologie der Wirbelsaüle, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1939, vol. 9, pp. 216-429.

2. Keyes, D. C., and Compere, E. L.: The Normal and Pathological Physiology of the Nucleus Pulposus of the Intervertebral Disc: An Anatomical, Clinical and Experimental Study, J. Bone & Joint Surg. **14**:897, 1932.

another factor in the causation of pain in the back. The extensive literature on these various lesions in the lumbar region has been recently reviewed by Saunders and Inman,[3] and by me [4] after an anatomic and roentgenologic study of the lumbar portion of 100 adult human spines.

It is my purpose in this communication to analyze the degenerative changes in the cervical portion of the spines of 50 adult human cadavers. Features of "discogenetic disease" which occur in the cervical region are less well described than those occurring elsewhere in the spine. A few authors,[5] in recording clinical and roentgenologic observations, have stressed the association of segmental neuritis (as evidenced by pain in the shoulder, arm and precordial regions and by weakness and muscular atrophy) with thinning of the intervertebral spaces, subluxation of the articular facets, narrowing of the intervertebral foramens and formation of exostoses on the anterior and lateral borders of the vertebral bodies of the cervical part of the spine.

PATHOLOGIC AND ANATOMIC ANALYSIS OF THE CERVICAL PORTION OF THE SPINES OF FIFTY ADULT HUMAN CADAVERS

The entire cervical and the upper part of the thoracic region of the spine were removed from 50 male cadavers whose ages varied from 45 to 80 years, with an average of 56 years. These were studied grossly after the removal of all paravertebral soft tissues and then were sectioned in the midsagittal plane.

Changes in the intervertebral disk were noted in 38, or 76 per cent, of the specimens and most frequently involved the lower cervical segments (between the third and the fourth cervical in 8, the fourth and the fifth cervical in 28, the fifth and the sixth cervical in 38, the sixth and the seventh cervical in 18 and between the seventh cervical and the first thoracic in 6). These changes consisted of varying stages of fibrillation, fissuring, brown degeneration, narrowing and ossification, and were associated with proportionate stages both of sclerosis of the adjacent vertebral spongiosa and of marginal bony proliferation. Such

3. Saunders, J., and Inman, V. T.: The Intervertebral Disc: Collective Review, Surg., Gynec. & Obst. **69**:14, 1939.

4. (*a*) Horwitz, T., and Smith, R. M.: An Anatomical, Pathological and Roentgenological Study of the Intervertebral Joints of the Lumbar Spine and of the Sacroiliac Joints, Am. J. Roentgenol. **43**:173-186 (Feb.) 1940. (*b*) Horwitz, T.: Lesions of the Intervertebral Disk and Ligamentum Flavum of the Lumbar Vertebrae: Anatomic Study of Seventy-Five Human Cadavers, Surgery **6**:410, 1939.

5. (*a*) Turner, E. L., and Oppenheimer, A.: A Common Lesion of the Cervical Spine Responsible for Segmental Neuritis, Ann. Int. Med. **10**:427, 1936. (*b*) Oppenheimer, A., and Turner, E. L.: Discogenetic Disease of the Cervical Spine with Segmental Neuritis, Am. J. Roentgenol. **37**:484, 1937.

exostosis formation, present in 35, or 70 per cent, of the specimens, was most advanced in the anterolateral portion of the vertebral body and involved especially the lower cervical vertebrae (third cervical in 4, fourth cervical in 14, fifth cervical in 28, sixth cervical in 35, seventh cervical in 35 and first thoracic in 10). Protrusion of intervertebral disk material into the spongiosa of the adjacent vertebral bodies was noted only once (between the fifth and the sixth cervical vertebra).

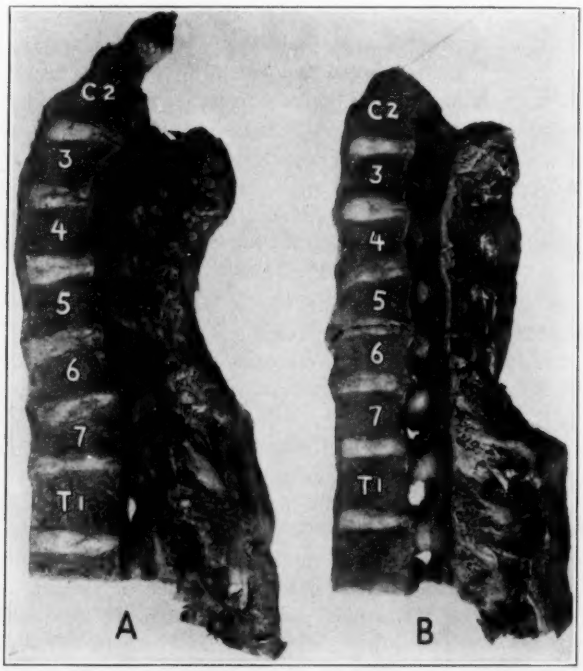

Fig. 1.—Degenerative changes involving the intervertebral disks. *A*, degeneration in the disks between the fifth and the sixth, the sixth and the seventh cervical and the seventh cervical and the first thoracic vertebra, associated with narrowing, fibrillation and "brown degeneration." The disk between the sixth and the seventh cervical vertebra is ossified anteriorly and associated with compression of the seventh cervical body. *B*, similar changes in the disks between the fourth and the fifth, the fifth and the sixth and the sixth and the seventh cervical vertebra. There is fissuring of the disk between the fifth and the sixth cervical segment, associated with anterior and posterior marginal proliferation.

Ossification of the intervertebral disk accompanied by fusion of the adjacent vertebral bodies was observed in three instances (once each between the fifth and the sixth cervical, the sixth and the seventh cer-

vical and the seventh cervical and the first thoracic vertebra) (figs. 1 through 5).

Narrowing of the entire intervertebral disk was associated with loss of the normal anterior curvature of the cervical spine and with *widening* of the intervertebral foramens. Loss of the posterior portion of the disk was associated with exaggerated cervical lordosis and with *narrowing* of the intervertebral foramens. Experimentally, the approxi-

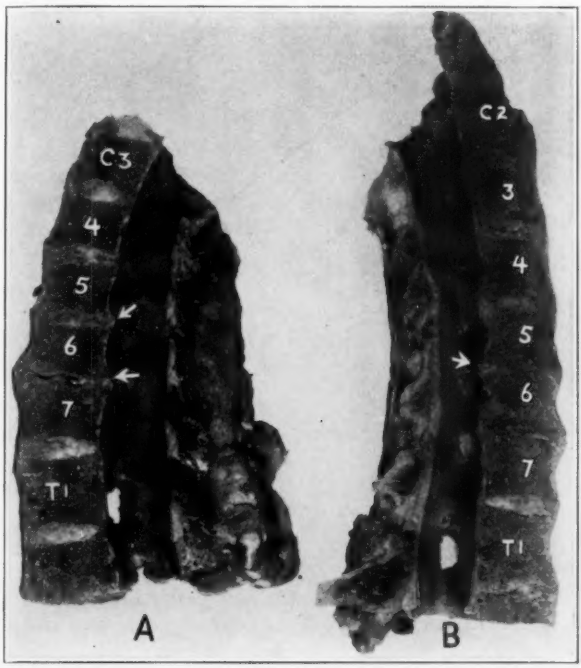

Fig. 2.—Degenerative changes involving the intervertebral disks of all the cervical vertebrae (*A* and *B*). The changes are most marked between the fifth and the sixth and between the sixth and the seventh cervical segment and are associated with anterior and posterior lipping of the upper and the lower margin of the vertebral bodies. The posterior osteophytes and intervertebral disks protrude into the spinal canal and encroach on the lumens of the respective intervertebral foramens.

mation of two normal adjacent vertebrae, after removal of the entire intervening disk, is followed by widening of the intervertebral foramens and not by narrowing. Diminution of the lumen of an intervertebral foramen was more frequently due to encroachment on its anterior surface by posterior lipping of the adjacent vertebral bodies, and to

encroachment on its posterior surface by marginal proliferation of the articular facets covered by ligamentum flavum of normal thickness. Such changes were evident in 20, or 40 per cent, of the specimens (between the third and the fourth cervical vertebra in 4, the fourth and the fifth cervical in 20, the fifth and the sixth cervical in 20, the sixth and the seventh cervical in 16, and the seventh cervical and the first thoracic in 4) (figs. 2, 4 and 5). "Posterior displacement" of one vertebra on another was seen once, the posterior margin of the body of

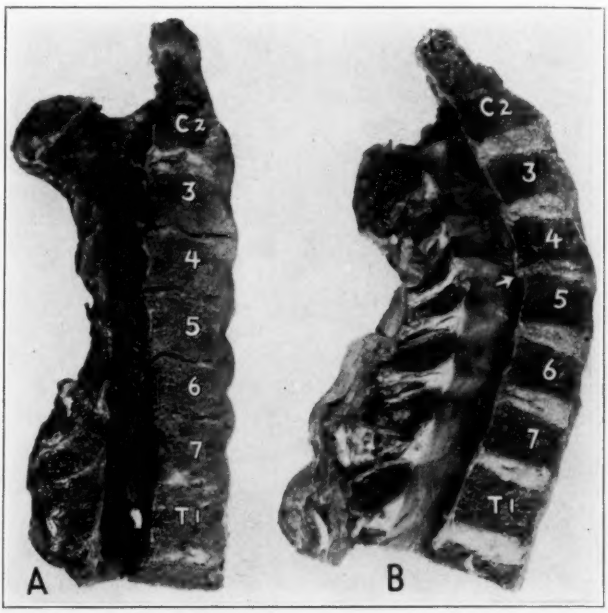

Fig. 3.—*A*, advanced degeneration of all the intervertebral disks, with approximation of the vertebral bodies and loss of the normal anterior curvature of the cervical spine. *B*, narrowing of the disk between the fourth and the fifth cervical segment, associated with ⅛ inch (0.32 cm.) "posterior displacement" of the body of the fourth cervical on the fifth. No congenital defects are present.

the fourth cervical vertebra lying ⅛ inch (0.32 cm.) posterior to the corresponding margin of the fifth cervical vertebra. There was no associated congenital defect, but there were narrowing and advanced degeneration of the intervening disk (fig. 3). No instance of anterior spondylolisthesis was observed. There were no secondary (accessory) epiphyses of the articular or spinous processes of any of the cervical vertebrae.

ROENTGENOGRAPHIC OBSERVATIONS ON THE CERVICAL PORTION OF THE SPINES OF TWENTY-FIVE ADULT HUMAN CADAVERS

Roentgenograms of the cervical and dorsal portions of the spines of 25 cadavers were made in the anteroposterior, lateral and right and left oblique (45 degrees) planes. Conclusions as to the relative merit of roentgenography in the diagnosis of degenerative lesions in the cervical

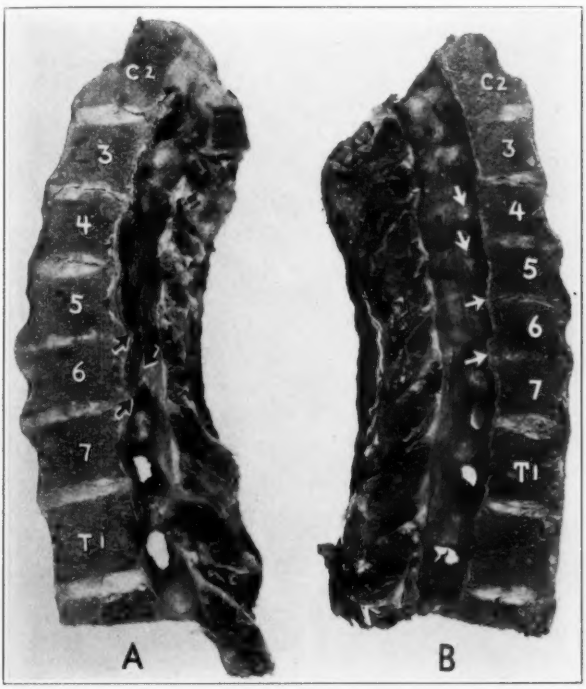

Fig. 4.—*A* and *B*, degenerative changes (narrowing, fibrillation, fissuring and "brown degeneration") involving all of the cervical intervertebral disks, and most advanced between the fifth and the sixth and between the sixth and the seventh cervical body, where there is associated anterior and posterior lipping. These posterior bony and disk protrusions are visibly narrowing the lumens of the respective intervertebral foramens. The anterior protrusions of the ligamentum flavum due to underlying marginal proliferation of the articular facets, are well visualized.

part of the spine were identical with those reported after a similar study of the lumbar portion of the spines of 25 human adults.[4a]

Anatomic and roentgenographic observations were specifically made of the articular processes and zygapophysial joints in the cervical part of

the spine. In a previous communication [4a] I concluded that the roentgenograms of the lumbar region of the spine taken in the 45 degree oblique plane, as advocated by a number of authors for the visualization of the articular facets and zygapophysial joints, must be evaluated with caution. The frequency in the lumbar vertebrae of curvature of

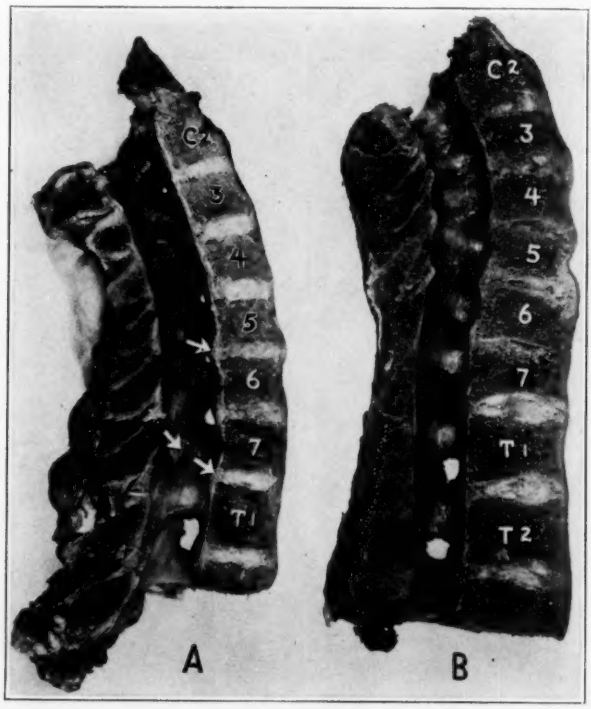

Fig. 5.—*A*, degenerated intervertebral disks between the fifth and the sixth and between the sixth and the seventh cervical vertebra. These disks and posterior osteophytes at the adjacent vertebral margins bulge posteriorly and encroach on the respective foramens. Anterior bulge of the ligamentum flavum due to marginal proliferation of the underlying articular facets diminishes the lumen of the intervertebral foramen between the seventh cervical and the first thoracic vertebra. The articular facets between the first and the second thoracic vertebra have been denuded to demonstrate the relation of these vertebrae to the foramen. *B*, marked osteoporosis of the vertebrae, associated with advanced degenerative changes in the cervical intervertebral disks. There is compression of the bodies of the sixth and the seventh cervical vertebra. The anterior portion of the disk between the fifth and the sixth cervical segment extends into the adjacent spongiosa above and below, while that between the sixth and the seventh cervical vertebra is ossified anteriorly. The intervertebral disks in the thoracic region, although degenerated, are expanded at the expense of the height of the adjacent osteoporotic vertebral bodies.

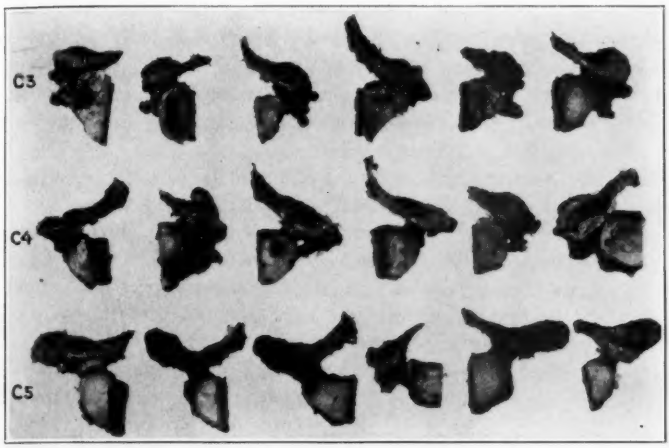

Fig. 6.—Superior facets of a number of third cervical (top row), fourth cervical (middle row) and fifth cervical (bottom row) vertebrae.

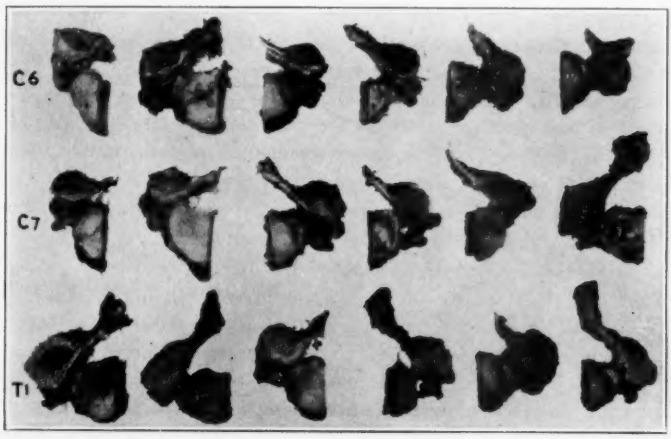

Fig. 7.—Superior articular facets of a number of sixth cervical (top row), seventh cervical (middle row) and first thoracic (bottom row) vertebrae. All the facets in figures 6 and 7 face cephalad (differing to varying degrees in the unmacerated specimens because of the normal anterior curvature of the cervical spine). The superior facets of all the cervical vertebrae are facing dorsalward. In the first thoracic segments, the first and second specimens from the left and the last one on the right face outward and dorsalward (thoracic type). Degenerative changes in the articular cartilage and marginal bony proliferation of the facets are most marked in the lower cervical and the first thoracic vertebrae.

the articular facet surface and of variation of the zygapophysial joint angle from the normal size of 45 degrees from the sagittal plane, makes impossible the penetration of the roentgen rays in a plane parallel to the joint space. Thus a summation of shadows is created on the roentgenogram which may falsely be interpreted as indicative of pathologic alteration when no such change is present.

These anatomic variations do not occur in the cervical region. The facet surfaces are always flat, and while the articular surfaces face at a variable degree cephalad (superior facet) and caudad (inferior facet), they invariably are directed dorsalward (superior facet) and ventralward (inferior facet) (figs. 6 and 7). In the making of a roentgenogram of a direct lateral view of the cervical portion of the spine, the roentgen rays therefore penetrate parallel to the articular surfaces. Narrowing, clouding and obliteration of the joint space, irregularity of the articular margins, sclerosis of the adjacent bones and marginal proliferation of the facets are indicative of pathologic changes. Such roentgenographic findings were most frequently noted in the lower part of the cervical region of the spine and were usually associated with degenerative changes in the intervertebral disks and vertebrae.

Since the facets between the atlas and the epistropheus converge so that the inferior facets of the first cervical vertebrae face downward and medialward, they are best visualized on the anteroposterior view through the open mouth. The facets between the seventh cervical and the first thoracic vertebra are in a transitional zone and may be of either the cervical type or the thoracic type (articular surfaces 20 degrees anterior to the coronal plane), and therefore the roentgenograms must be made in both planes (fig. 7). Roentgenograms of the 45 degree oblique views of the cervical portion of the spine visualize best the size and shape of the intervertebral foramens.

COMMENT

Differential Diagnosis of Pain in the Neck, Shoulder and Upper Extremity.—Oppenheimer and Turner [5] ascribed certain cases of segmental neuritis in elderly persons to the thinning of one or more intervertebral spaces of the cervical portion of the spine accompanied by consequent unilateral or bilateral narrowing of the corresponding intervertebral foramens and by compression of nerve roots. Discogenetic disease in the cervical part of the spine may therefore be associated with discomfort, muscular weakness and atrophy in the upper extremities, shoulder girdle, neck and precordium. Constriction of the intervertebral foramen may be consequent on inflammatory and degenerative changes in the zygapophysial joints, even with the intervertebral disks uninvolved. This concept parallels the association, suggested by many authors, between degenerative lesions in the lumbar portion of the spine and backache with pain referred to the lower extremities.

The relation of cervical osteoarthritis to root pain and radicular sensory alterations and the importance of differentiating this syndrome from visceral diseases which it may simulate were previously stressed by Gunther and Kerr.[6] Nathan,[7] after the experimental production of nonsuppurative arthritis in animals, concluded that pain in spondylitis may be referred from nerve roots which are compressed as they leave their bony outlets either by inflamed ligaments and capsules or by adhesions, in the infectious variety of spondylitis, and by pressure of osteophytes and of thickened soft tissues in the hypertrophic variety. Gunther and Sampson,[8] Nachlas[9] and Hanflig[10] noted that left-sided segmental neuritis due to cervical arthritis may simulate cardiac disease because of pain referred to the precordium, the left shoulder and the left upper extremity. Bailey and Casamajor,[11] Parker and Adson[12] and Morton[13] reported that soft tissue and bony overgrowth in cervical osteoarthritis may encroach on the spinal canal and simulate other extramedullary lesions of the spinal cord.

The symptoms and signs of segmental neuritis in hypertrophic arthritis of the cervical portion of the spine are not unlike those of a number of other pathologic conditions, viz., the cervical rib syndrome, brachialgia associated with a low position of the shoulder girdle, the scalenus anticus syndrome, brachial plexus neuritis, lesions of the shoulder joint (arthritis, bursitis, lesions of the supraspinatus tendon) and fracture of the clavicle or the first rib. Nathanson[14] indicated that

6. Gunther, L., and Kerr, W. J.: The Radicular Syndrome in Hypertrophic Osteo-Arthritis of the Spine: An Analysis of Thirty Cases, Arch. Int. Med. **43**: 212 (Feb.) 1929.

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9. Nachlas, I. W.: Pseudo-Angina Pectoris Originating in the Cervical Spine, J. A. M. A. **103**:323 (Aug. 4) 1934.

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11. Bailey, P., and Casamajor, L.: Osteoarthritis of the Spine as a Cause of Compression of the Spinal Cord and Its Roots, with Report of Five Cases, J. Nerv. & Ment. Dis. **38**:588, 1911.

12. Parker, H. L., and Adson, A. W.: Compression of the Spinal Cord and Its Roots by Hypertrophic Osteoarthritis: Diagnosis and Treatment, Surg., Gynec. & Obst. **41**:1, 1925.

13. Morton, S. A.: Localized Hypertrophic Changes in the Cervical Spine with Compression of the Spinal Cord or of Its Roots, J. Bone & Joint Surg. **18**:893, 1936.

14. Nathanson, L.: Pulmonary Apical Tumefaction Simulating Bursitis: Necessity for Routine Chest Examination in Patients with Shoulder Pain, Quart. Bull., Sea View Hosp. **4**:326, 1939.

tumors at the apex of the chest,[15] because of identical symptoms, may mask themselves by the incidental presence of lesions in the cervical portion of the spine or in the shoulder region.

The scalenus anticus syndrome, described by Ochsner, Gage and DeBakey,[16] who attributed its original concept and successful treatment by scalenotomy to Naffziger,[17] is characterized by the clinical picture of cervical rib in the absence of such a supernumerary rib, and is due to spasm and hypertrophy of the scalenus anticus muscle, which serves to compress the lower trunks of the brachial plexus and the subclavian artery against the first rib. While this condition may be primary, it is often secondary, according to Freiberg [18] and Bishop.[19] Cervical arthritis and lesions of the shoulder girdle may aggravate and perpetuate their symptoms and signs by initiating spasm of the scalenus anticus, and this cycle may or may not be broken by the successful therapy of the underlying lesion.

Peripheral Vascular Phenomena Associated with Spondylitis.—Because of the known relief of articular symptoms in chronic infectious arthritis after treatment with general and local measures to induce peripheral vasodilatation, Rowntree and Adson [20] recommended sympathetic ganglionectomy for those types associated with abnormal alterations of peripheral vascular tonus. Craig and Kernohan [21] failed to observe any significant histologic changes in the sympathetic ganglions removed in 46 such cases; these authors suggested that the ganglions act merely as relay stations for impulses from higher centers.

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15. Ray, B. S.: Tumors at the Apex of the Chest, Surg., Gynec. & Obst. **67**:577, 1938.

16. Ochsner, A.; Gage, M., and DeBakey, M.: Scalenus Anticus (Naffziger) Syndrome, Am. J. Surg. **28**:669, 1935.

17. Naffziger, H. C.: Neuritis of the Brachial Plexus Mechanical in Origin, Surg., Gynec. & Obst. **67**:722, 1938.

18. Freiberg, J. A.: The Scalenus Anterior Muscle in Relation to Shoulder and Arm Pain, J. Bone & Joint Surg. **20**:860, 1938.

19. Bishop, W. A.: Calcification of the Supraspinatus Tendon: Cause, Pathologic Picture and Relation to the Scalenus Anticus Syndrome, Arch. Surg. **39**:231 (Aug.) 1939.

20. Rowntree, L. G., and Adson, A. W.: Bilateral Lumbar Sympathetic Ganglionectomy and Ramisectomy for Polyarthritis of the Lower Extremities, J.A.M.A. **88**:694 (March 5) 1927; Polyarthritis: Further Studies on the Effects of Sympathetic Ganglionectomy and Ramisectomy, ibid. **93**:179 (July 20) 1929; Bilateral Lumbar and Thoracic Sympathetic Ganglionectomy and Ramisectomy for Polyarthritis of the Lower and the Upper Extremities, Tr. A. Am. Physicians **44**:221, 1929; The Surgical Indications for Sympathetic Ganglionectomy and Trunk Resection in the Treatment of Chronic Arthritis, Surg., Gynec. & Obst. **50**:204, 1930.

21. Craig, W. M., and Kernohan, J. W.: The Surgical Removal and Histologic Studies of Sympathetic Ganglia in Raynaud's Disease, Thrombo-Angiitis Obliterans, Chronic Infectious Arthritis and Scleroderma, Surg., Gynec. & Obst. **56**:767, 1933.

Stewart,[22] while performing a lumbar sympathectomy to relieve intermittent claudication and paresthesias in the lower extremities of a 61 year old man, observed the trunk involved in a mass of tissue surrounding the hypertrophic process between the fourth and the fifth lumbar vertebra, and he noted improvement, after extirpation of the left lumbar sympathetic trunk, in the peripheral circulation of the ipsilateral lower extremity.

Lipshutz and Naide[23] called attention to the writings of Hesse, Zaiceva and Vinogradov,[24] who noted the calorimetric changes in the skin of the lower extremity resulting from irritation or pressure on the lumbar portion of the ganglionated sympathetic cord and its communicating rami. Any lesion which presses on or irritates the lumbar portion of the ganglionated cord may effect change in the temperature of the lower extremity on the side on which the lesion occurs. Irritation by moderate pressure may produce peripheral vasoconstriction, but when the ganglions become destroyed and impulses are interrupted, peripheral vasoconstriction is followed by peripheral vasodilatation. Lipshutz and Naide illustrated such peripheral vascular changes resulting from pressure on the lumbar sympathetic cord in 3 cases, one with a carcinoma of the transverse colon involving the posterior portion of the parietal wall, another with a mass of retroperitoneal lymph nodes and a third with an enormously thickened terminal ileum due to chronic inflammatory disease.

I noted that in the lumbar portion of the spines of a number of adult cadavers in which advanced marginal osteophytes involved the anterolateral portion of the vertebral bodies, the lumbar sympathetic ganglionated cord was frequently involved in these soft tissue and bony masses, and that frequently a segment of the sympathetic trunk was markedly stretched over an enlarged osteophyte. May this relation explain, in the light of the clinical observations of Lipshutz and Naide, the peripheral vascular phenomena occasionally noted in the lower extremities of patients with the atrophic and hypertrophic varieties of spondylitis, as well as the relief of peripheral vascular symptoms after sympathectomy in properly selected cases?

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22. Stewart, S. F.: Relation of the Sympathetic Nervous System to Hypertrophic Arthritis, J. Bone & Joint Surg. **13**:848, 1931.

23. Lipshutz, B., and Naide, M.: Clinical Significance of Calorimetric Changes in the Lower Extremity, Arch. Surg. **38**:412 (March) 1939.

24. Hesse, E.: Ein neues calorimetrisches, durch Druck auf den Sympathicus hervorgerufenes Symptom retroperitonealer raumbeschränkender Erkrankungen, Klin. Wchnschr. **8**:1360, 1929. Zaiceva, A.: Ueber das Hesse'sche Symptom bei Retroperitonealtumoren, Zentralbl. f. Chir. **59**:2685, 1932. Vinogradov, I. P.: Das calorimetrische Symptom Hesses bei Geschwülsten und anderen raumbeschränkenden Erkrankungen im Retroperitonealraum, Deutsche Ztschr. f. Chir. **246**:634, 1936; cited by Lipshutz and Naide.[23]

I also observed the proximity of the stellate and the second thoracic sympathetic ganglions to the costovertebral articulations of the first and the second rib respectively, the ganglions overlying the anterior surfaces of the joints in intimate contact with the joint capsule. May this anatomic relationship explain the peripheral vascular phenomena in the upper extremities occasionally encountered in patients with infectious spondylitis involving the cervicothoracic portion of the spine, and in some patients with hypertrophic arthritis affecting the same region? Proliferative and degenerative changes in the costovertebral joints were associated with comparable lesions in the cervical and thoracic portions of the spine in a number of my specimens, and although such changes were conspicuous in the joint between the rib and the vertebral body (costocentral articulation), they were infrequently found in the articulation between the tubercle of the rib and the transverse process (costotransverse articulation). In some of the specimens the stellate and the second thoracic ganglions were visibly impinged on by extensive marginal bony proliferation and thickening of soft tissue involving the related costovertebral articulations.

Since lesions in the cervical part of the spine may at times initiate spasm of the scalenus anticus muscle,[18] the associated vascular phenomena in the upper extremities in these cases may be due in part or entirely to stimulation of the sympathetic nerves which enter the arm via the lowest trunk of the brachial plexus (Todd [25]). The observation by Telford and Stopford [26] of a separate ramus of unmyelinated sympathetic fibers in the inferior part of the lowest plexus trunk overlying the first rib has not been confirmed by Dr. Andrew J. Ramsay and me after a similar study of the lower part of the trunk of 12 brachial plexuses. The unmyelinated sympathetic fibers were diffused uniformly throughout the nerve trunk. The anomaly in the lower extremity comparable to the scalenus anticus syndrome is spasm of the piriformis muscle associated with the sciatic syndrome. That such spasm of the piriformis muscle may be incidental to the lesions of the lumbar spine, the lumbosacral area and the sacroiliac joints has been suggested by Freiberg.[27]

SUMMARY

The occurrence of degenerative lesions of the intervertebral disks and vertebrae in the cervical portion of the spine follows a progressive sequence of events. These changes are identical with those occurring

25. Todd, T. W.: The Arterial Lesion in Cases of Cervical Rib, J. Anat. & Physiol. **47**:250, 1912-1913.

26. Telford, E. D., and Stopford, J. S. B.: The Vascular Complications of Cervical Rib, Brit. J. Surg. **18**:557, 1931.

27. Freiberg, A. H.: Sciatic Pain and Its Relief by Operations on Muscle and Fascia, Arch. Surg. **34**:337 (Feb.) 1937.

in the thoracic and the lumbar portion of the vertebral column and are found most frequently in the lower segments of the cervical part of the spine. The concept of segmental neuritis, consequent on mechanical or inflammatory irritation of the nerve roots, as a cause of symptoms and signs referable to the neck, shoulder and upper extremity, parallels the relation which has been suggested between similar degenerative lesions of the lumbar portion of the spine and the "low back" syndrome referable to the lower extremities.

The roentgenograms of the cervical portion of the spine made in the lateral and the 45 degree oblique plane may be relied on to visualize accurately pathologic changes involving the articular processes, zygapophysial joints and intervertebral foramens, because few anatomic variations occur in this region.

The diagnosis of segmental neuritis incidental to "discogenetic disease" of the cervical part of the spine requires a cautious exclusion of a number of other pathologic conditions in the neck, shoulder region and apex of the chest. The interrelation of several of these conditions in the same person may enhance the difficulty of differential diagnosis.

Peripheral vascular phenomena are not infrequently evident in patients with the hypertrophic variety of spondylitis. The suggestion, based on certain observations on the human cadaver, is made that these alterations in vascular tonus may be due to direct mechanical or inflammatory irritation of the sympathetic ganglionated cord. Peripheral vasomotor changes in those cases in which there is complicating spasm of the scalenus anticus or of the piriformis muscle may be due in part or entirely to direct irritation of the sympathetic nerves within the nerve trunks which are compressed.

GLOMERULAR NEPHRITIS FOLLOWING INFECTIONS OF THE SKIN

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While it is generally accepted that acute infection caused by streptococci precedes acute glomerular nephritis in the majority of cases, the exact course of events linking the infection with the renal disturbance is far from clear. Nor is it known whether once the nephritis has manifested itself, chronic infection remains an important agent in prolonging the disease. Authorities differ in the relative emphasis they place on the role of infection in this respect. Among protagonists of the etiologic importance of foci of infection is Kollert,[1] who distinguished two types of infection. One is the "primary focus," a chronic, often long-standing obscure process, situated perhaps in a paranasal sinus, which renders the subject peculiarly reactive to the machinations of subsequent acute invasion by the same organism. In the latter, "precipitating infection," the second of the two types, Kollert saw a trigger mechanism which sets off the initial attack of nephritis, the stage having already been set by the "primary focus." Kollert asserted that, in order to abort the nephritis, it is mandatory not only to remove any residue of the acute precipitating infection, but also to find and exterminate the less obtrusive "primary focus," which is only rarely identical with the precipitating process. He stated the belief that usually the persistence of the urinary abnormalities is evidence that there is still in the body some remnant of infection. Longcope [2] has also suggested that the progression of nephritis to a subacute or chronic stage may be accompanied by persistence or exacerbations of the infection.

There is no general agreement, however, that the persistence of infection is the explanation for the evolution of chronic nephritis, since the removal of all ascertainable foci may not change an unfavorable

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1. Kollert, V.: Grundlagen der ätiologischen Behandlung der Nierenentzündung, Leipzig, Franz Deuticke, 1929; cited by Volhard, F.: Zentralbl. f. inn. Med. **51**:301-308 (April) 1930.

2. (*a*) Longcope, W. T.: Some Observations on the Course and Outcome of Hemorrhagic Nephritis, Internat. Clin. **1**:1-16 (March) 1938. (*b*) Longcope, W. T.; O'Brien, D. P.; McGuire, J.; Hansen, O. C., and Denny, E. R.: Relationship of Acute Infections to Glomerular Nephritis, J. Clin. Investigation **5**:7-30 (Dec.) 1927.

course; this has been pointed out by Winkenwerder and his confrères [3] at the Johns Hopkins Hospital. In reviewing Kollert's monograph, Volhard,[4] who himself subscribed to a theory of the relationship of acute nephritis to infection quite similar to that of Kollert, stated his approval of that author's zeal in eradicating foci of infection in the early stages of nephritis, but he was dubious as to the efficacy of such procedures in the chronic stage. Addis,[5] while also acknowledging an important initial role of the acute infection, has been a proponent of the self-styled "gloomy hypothesis" that "the continuance over years and decades of a slow disintegration of the architecture of the kidney might be a result of the structural disorganization produced in the initial stage of the disease." By analogy he cited the evidence of the long-continued effects on the kidney of experimental acute uranium poisoning. Further, one might point to the chronic nephritis in rats which has been reported as following injections of a nephrotoxic serum.[6] However, Addis commented that his own hypothesis is at least partially contradicted by the fact that one cannot consistently forecast the evolution of an acute attack of nephritis in human beings to chronicity or to recovery merely on the basis of the intensity of the disease in its initial stage.

Since it is admittedly extremely difficult to be sure of the complete extinction of any infection involving the respiratory tract, it comes to mind that information on the importance of chronic infection in maintaining pathologic activity in the kidneys might be obtained from the study of cases in which glomerular nephritis has followed infections of the skin or of the subcutaneous tissues. The superficial location of the inflammatory process enables the observer to ascertain with some accuracy the moment at which the cutaneous lesion is healed. If the activity of the nephritis is maintained by an infection of the skin, one would expect eventual complete healing of the renal lesion to follow healing of the skin. Further, one would prophesy a uniformly excellent prognosis for complete recovery in this group of cases as compared with

3. Winkenwerder, W. L.; McLeod, N., and Baker, M.: Infection and Hemorrhagic Nephritis, Arch. Int. Med. **56**:297-326 (Aug.) 1935.

4. (*a*) Volhard, F.: Die doppelseitigen hämatogenen Nierenerkrankungen, in von Bergmann, G., and Staehelin, R.: Handbuch der inneren Medizin, Berlin, Julius Springer, 1931, vol. 6, pt. 2. (*b*) Kollert.[1]

5. Addis, T.: Haemorrhagic Bright's Disease: I. Natural History, Bull. Johns Hopkins Hosp. **49**:203-224 (Oct.) 1931; II. Prognosis, Etiology, and Treatment, ibid. **49**:271-285 (Nov.) 1931.

6. Smadel, J. E.: Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum: I. Preparation and Immunological Studies of Nephrotoxin, J. Exper. Med. **64**:921-942 (Dec.) 1936; III. Pathological Studies of the Acute and Chronic Disease, ibid. **65**:541-555 (April) 1937. Smadel, J. E., and Farr, L. E.: Experimental Nephritis in Rats Induced by Injection of Anti-Kidney Serum: II. Clinical and Functional Studies, ibid. **65**:527-540 (April) 1937.

those in which glomerular nephritis is associated with persistent or recurring infections of the respiratory tract, since it should be easier to eradicate infections of the skin than infections of the nasopharynx. To test this hypothesis, a search of the literature concerning relevant cases has been made and the reports summarized. Also a study has been made of the records of a selected group of patients treated in the Johns Hopkins Hospital whose disease appeared following an infection of the skin. That there is relatively little information on this subject in the American literature lends greater interest to the investigation.

TABLE 1.—*Relative Frequency of Infections of the Skin Preceding Glomerular Nephritis, Tabulated from Various Authors*

Observer	Total Cases of Nephritis	Cases Following Cutaneous Infection	Percentage	Type of Cutaneous Infection	Constitution of Whole Group
Bluhm [20]	140	2	1.4	Erysipelas, 1; impetigo, 1	Patients of all ages
Kaumheimer [7]	223	21	9.4	Impetigo	Children
Volhard and Fahr [10a]	204	22	11	Erysipelas, 5; miscellaneous, 17	Chiefly adults
Hill [12]	75	4	5.3	Impetigo	Children
Osman [13]	235	11	4.7	Skin and scalp wounds	Children and young adults
Southby and Stanton [14]	103	18	17	Chiefly impetigo	Children
Clausen [15]	102	1	1	Erysipelas	Children
Kollert [1]	80	..	5-15	Not stated	Not stated
Van Slyke and others [16]	50	0	0	.....	Chiefly adults
Guild [11]	34	1	2.9	Furunculosis	Children
Addis [5]	..	..	20	Infected wounds	Not stated
Lichtwitz [17]	167	28	17	Miscellaneous	Not stated
Sutton [9]	18	5	28	Impetigo	Not stated
Richter [18]	100	1	1	Erysipelas	Adolescents and adults
Present series	153*	11	7.2*	Miscellaneous	Children and adults

*Nephritis of type A only.

REVIEW OF THE LITERATURE

Relative Importance of Infections of the Skin in the Causation of Nephritis.—It should be emphasized at once that of all the infections of the skin complicated by nephritis, impetigo has been the agent most frequently discussed in the papers to which I have had access. Kaumheimer [7] thoroughly reviewed the earlier literature on "impetigo-nephritis" and presented a relatively large series of his own cases.[7a]

7. Kaumheimer, L.: Ueber akute Nephritis bei Kindern nach impetiginösen Hauterkrankungen, Monatschr. f. Kinderh. **10**:139-153, 1912.

7a. The subject of impetigo-nephritis was recently reviewed by Silvers, S. H.: Impetigo Contagiosa Complicated by Acute Nephritis, New York State J. Med. **39**:1093-1095 (June 1) 1939.

Phillips [8] was one of the first to draw attention to the syndrome in this country. More recently Sutton [9] reported its occurrence in 5 children. Numerous other examples are recorded in the foreign literature on this specific subject and also in the more general papers on glomerular nephritis. The significance of the preeminence of impetigo-nephritis in the group of cases reported in this paper will be pointed out later in the sections on age incidence, bacteriology and prognosis. Monographs on nephritis [10] describe the disease as following cutaneous infections other than impetigo, such as suppurating wounds of the skin, furunculosis and pyogenic infections superimposed on scabies and eczema; doubtless many so-called cases of impetigo are actually instances of pyoderma complicating other conditions, such as eczema.

That infection of the skin appears to play an important part in the production of glomerular nephritis may be seen from table 1. It should be noted that Addis' figures [5] dealt only with those cases of nephritis (83 per cent of all his cases) in which there was some ascertainable antecedent infection. Guild's series [11] represented a group selected because of survival of the acute stage of nephritis. The data of Volhard and Fahr,[10a] Hill,[12] Osman,[13] Southby and Stanton,[14] Clausen,[15] Kollert,[1] Van Slyke and others,[16] Guild,[11] Addis,[5] Lichtwitz [17] and Richter [18] are taken from general articles on glomerular nephritis in which there was

8. Phillips, J.: Nephritis, a Complication of Impetigo, with Report of Two Cases, Cleveland M. J. **9**:686-691 (Sept.) 1910.

9. Sutton, L. E., Jr.: Nephritis Complicating Impetigo, South. M. J. **27**: 798-802 (Sept.) 1934.

10. (*a*) Volhard, F., and Fahr, T.: Die Brightischer Nierenkrankheit, Berlin, Julius Springer, 1914. (*b*) Munk, F.: Pathologie und Klinik der Niereneerkrankungen, Berlin, Urban & Schwarzenberg, 1925, p. 381. (*c*) Volhard,[4a] p. 1245.

11. Guild, H. G.: The Prognosis of Acute Glomerular Nephritis in Childhood, Bull. Johns Hopkins Hosp. **48**:193-211 (April) 1931.

12. Hill, L. W.: Studies in the Nephritis of Children, Am. J. Dis. Child. **17**: 270-294 (April) 1919.

13. Osman, A. A.: The Aetiology and Prognosis of Acute Nephritis in Children and Young Adults, Guy's Hosp. Rep. **75**:306-312 (July) 1925.

14. Southby, R., and Stanton, B. L.: Acute Nephritis in Children, with Special Reference to Renal Efficiency Tests, M. J. Australia **1**:127-133 (Jan. 30) 1926.

15. Clausen, S. W.: Nephritis in Children, Atlantic M. J. **29**:201-205 (Jan.) 1926.

16. Van Slyke, D. D., and others: Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy, Medicine **9**:257-386 (Sept.) 1930.

17. Lichtwitz, L.: Die Praxis der Nierenkrankheiten, Berlin, Julius Springer, 1934, p. 251.

18. Richter, A. B.: Prognosis in Acute Glomerular Nephritis, in Medical Papers Dedicated to Henry Asbury Christian, Baltimore, Waverly Press, Inc., 1936, pp. 268-282.

no special emphasis placed on infections of the skin. Sommer,[19] reporting on impetigo-nephritis in children, stated that nephritis of this origin is as common as that following tonsillitis. In explanation of the relatively low incidence reported by Bluhm [20] I can remark only that her paper was written at a period when no very clear distinction was made between glomerular nephritis and other forms of Bright's disease. One cannot immediately explain why none of Van Slyke's 50 cases and only 1 of Clausen's and 1 of Richter's fell into the group under consideration. There is apparently considerable variability in the incidence of this type of nephritis.

Age of Patients with Glomerular Nephritis Secondary to Infection of the Skin.—Since impetigo is more common in children than in adults, it is not unreasonable that writers on impetigo-nephritis emphasize that the latter syndrome is commonly one of childhood.[21] Husler [21b] stated the belief that this type of nephritis is seen most frequently in children between the ages of 4 and 7 years. Kaumheimer [7] noted that infants under 1½ years are relatively immune to impetigo-nephritis. Adults, however, may be affected; thus 5 of Hering's 7 patients were adults.[22] Nephritis secondary to a wound or to pyoderma may be seen at any age.

Bacteriologic Observations.—It appears that impetigo-nephritis may occur in epidemics. Husler [21b] observed glomerular nephritis in 6 of 16 patients with impetigo seen in the spring of 1915; Eichhorst,[23] in a family of 4 children with impetigo, found mild to severe nephritis in 3. No statistics have been encountered detailing the incidence of nephritis as a complication in a large series of cases of impetigo. Hering [22] and Phillips [8] each recovered a "streptococcus" from an impetigo pustule in a single case of impetigo-nephritis; Kohn [24] isolated diphtheroid organisms in 1 case. Reports on the causes of uncomplicated impetigo contagiosa itself are also somewhat inconclusive. It has been stated that both staphylococci and streptococci may cause impetigo and that the former are most commonly isolated in the United States, while the latter pre-

19. Sommer: Ueber die Häufigkeit und Eigenart der Impetigo-Nephritis im Kindesalter, Veröffentl a. d. Geb. d. Heeressanitäts **85**:178-186, 1931; abstracted, Zentralbl. f. Haut- u. Geschlechtskr. **39**:79-80, 1932.

20. Bluhm, A.: Zur Aetiologie des Morbus Brightii, Deutsches Arch. f. klin. Med. **47**:193-225, 1891.

21. (*a*) Maier, F.: Nephritis bei Impetigo contagiosa, München. med. Wchnschr. **64**:215 (Feb. 13) 1917. (*b*) Husler, J.: Zur Frage der Impetigo-Nephritis, Klin. Wchnschr. **1**:1826-1828 (Sept. 9) 1922. (*c*) Kaumheimer.[7]

22. Hering, E.: Impetigo-Nephritis, Zentralbl. f. inn. Med. **43**:633-636 (Sept. 30) 1922.

23. Eichhorst, H.: Ueber Impetigo-Nephritis, Deutsches Arch. f. klin. Med. **118**:462-475, 1916.

24. Kohn, H.: Impetigo-Nephritis, Berl. klin. Wchnschr. **58**:28-29 (Jan. 10) 1921; Zur Impetigo-Nephritis, ibid. **58**:131 (Feb. 7) 1921.

dominate in Europe.[25] Adamson,[26] however, stated the belief that impetigo is in all cases caused primarily by streptococci and that staphylococci represent merely secondary invaders.

Prodromal Period.—Although it is notoriously difficult to delimit exactly the prodromal period, several of those who have written on impetigo-nephritis have made statements as to the interval elapsing between the onset of the cutaneous infection and the first symptom of renal disease, usually edema. Kaumheimer [7] gave the interval as two to six weeks, Hering [22] as four weeks and Maier [21a] as three to four weeks. Husler [21b] stated that the nephritis appears usually at the height of the impetigo and less commonly after the healing of the skin. Cases have been reported in which the interval was only three days;[27] on the other hand, not uncommonly a case is reported in which the patient had suffered from episodes of impetigo for many years, only to manifest nephritis in the course of an involvement of the skin not apparently different from the previous uncomplicated attacks.[9] For comparison it is interesting to note that Winkenwerder, McLeod and Baker [3] found that of 41 cases of glomerular nephritis selected without reference to the type of preceding infection, in 80 per cent the disease developed after a prodromal period of seven to sixteen days.

Course of the Nephritis and Prognosis.—Glomerular nephritis following impetigo does not differ in its manifestations from glomerular nephritis secondary to scarlet fever, for instance, or to acute pharyngitis; the physical findings and the changes in the urine are identical. Kaumheimer [7] was unable to find any correlation between the severity or the location of the impetigo and the character of the subsequent nephritis. Many authors have emphasized the rapidity with which the signs of the nephritis clear after the healing of the infection of the skin, be it impetigo [21b] or other types of involvement of the skin.[10c] The prognosis is generally considered excellent,[28] most patients leaving the hospital after eight to twelve weeks' stay. In considering this reputedly bright outlook for impetigo-nephritis it must be recalled, however, that the prognosis for acute nephritis in children is notably better than that for the same disease in adults [11] and that the majority of the reported cases of impetigo-nephritis have concerned children; thus possibly the prognosis is governed not by the type of antecedent infection but merely by the age of the group of patients. Kauheimer [7] reported 2 fatalities in his series of 21 patients, or a mortality of 9.5 per cent; both deaths

25. Tachau, P.: The Bacteriology of Impetigo Contagiosa, Brit. J. Dermat. **50**:113-118 (March) 1938.

26. Adamson, H. G.: On the Bacteriology of Pemphigus Neonatorum, Brit. J. Dermat. **49**:93-99 (March) 1937.

27. Eichhorst.[23] Sutton.[9]

28. Hering.[22] Husler.[21b]

occurred in the presence of uremia early in the disease. Maier [21a] lost 2 patients in uremia, in a small series of 7 patients with impetigo-nephritis, and he thought, contrary to general opinion, that the prognosis for this type of nephritis should remain very guarded. Many of the patients reported by the authors cited as having recovered left the hospital still showing albumin and red cells in their urine and were not adequately followed up. In summary, the information at hand is inadequate to indicate definitely whether the outcome of glomerular nephritis following pyogenic infections of the skin differs in any way from that of nephritis secondary to infection at other sites.

PROTOCOLS

The cases which I shall now report from the adult medical service of the Johns Hopkins Hospital represent all the recorded examples of acute hemorrhagic nephritis following infections of the skin which have been observed in that service since 1923. They have been selected from a group of 153 cases of acute hemorrhagic nephritis which followed infection of various sorts and came under observation early in the course of the disease. The 153 cases comprise those in Longcope's [29] group 1 (of nephritis type A; i. e., the type of nephritis which follows an acute infection) in contradistinction to those in his group 2 (nephritis of type B, in which the onset is insidious). In only 2 of our 11 patients (M. B. and C. McK.) was there any ascertainable acute infection other than an infection of the skin immediately preceding the onset of the nephritis. Each patient was carefully examined for foci of infection other than those in the skin; in 7 patients the pharynx came under suspicion and in 3 patients the teeth. The urine of all the patients was sterile. Serologic tests for syphilis gave negative results for all patients save 3 (J. D., C. McK. and D. T.).

In these protocols the urinary phenolsulfonphthalein excretion is expressed as percentage excreted in two hours. The urea clearance determinations were performed according to the technic of Van Slyke,[30] no correction being made for size when the patient was a child. The formed elements in the urine are described as seen in an average high power field during the microscopic examination of a centrifuged speci-

29. Longcope, W. T.: (*a*) Studies of the Variations in the Antistreptolysin Titre of the Blood Serum from Patients with Hemorrhagic Nephritis: I. Control Observations on Healthy Individuals and Persons Suffering from Diseases Other than Streptococcal Infections, J. Clin. Investigation **15**:269-275 (May) 1936; II. Observations on Patients Suffering from Streptococcal Infections, Rheumatic Fever and Acute and Chronic Hemorrhagic Nephritis, ibid. **15**:277-294 (May) 1936; (*b*) footnote 2*a*.

30. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams and Wilkins Company, 1932, vol. 2.

men. In addition, Addis counts [31] were made on the urinary sediment from time to time. Quantitative determinations of urinary protein, when made, were performed according to the rather inaccurate technic of Esbach, save in association with an Addis count, when they were done according to the method of Shevky and Stafford [32] as modified by Peters and Van Slyke.[30] The upper limits of normal for the twelve hour Addis count have been considered as 425,000 red blood cells, 1,835,000 white blood cells, 4,270 casts, and 30 mg. of protein.[33] Longcope has described the technic of the serum antistreptolysin titrations in this group of cases; [29] I have considered 100 units the upper limit of normal. The blood pressure recorded for each patient on admission was the highest reading observed during the early days of the stay in the hospital. The patients were given an alkaline ash diet routinely; the fluid and salt intake was varied according to the degree of cardiac failure, edema and uremia.

CASE 1.—*Impetigo, moderately severe nephritis, recovery.*

M. B., a 9 year old white boy, was admitted on March 5, 1935, with the history that for two weeks he had had impetigo on his face and buttocks, for three days, generalized edema, and for two days, fever and sore throat. On admission his temperature was 102 F. and his blood pressure 130 systolic and 80 diastolic. There was healing impetigo on the face and buttocks, and there was a scarlatiniform rash on the trunk. There was slight generalized edema. The tonsils were large and red. The white blood cell count was 17,000. The specific gravity of the urine was 1.022. There was albuminuria (4 plus), with from 20 to 30 red blood cells, 5 white cells and casts of all sorts. The nonprotein nitrogen content of the blood was 27 mg. per hundred cubic centimeters, and the phenolsulfonphthalein excretion was 88 per cent. Material from the cutaneous lesions was not cultured. Cultures of material from the throat revealed beta streptococci persistently until a tonsillectomy was done, April 20, 1935; cultures of the tonsillar tissue removed at operation showed a practically pure growth of beta streptococci and minute beta streptococci. The patient had a low elevation of temperature during his stay, but otherwise improvement was rapid. The scarlatiniform rash disappeared immediately; by March 9 the edema had disappeared and the impetigo had healed. The urine cleared rapidly; an Addis count on May 6, 1935, the day of discharge, was normal save for 13,000 casts; the nephritis was regarded as healed. The urea clearance on May 3 was 90 per cent of the normal maximum. In May 1939, the urine showed no albumin, and the sediment was normal. (It is possible that this patient had true scarlet fever and that the nephritis was secondary to the scarlatina rather than to the impetigo.[33a])

31. Addis, T.: A Clinical Classification of Bright's Disease, J. A. M. A. **85:** 163-167 (July 18) 1925.

32. Shevky, M. C., and Stafford, D. D.: A Clinical Method for the Estimation of Protein in Urine and Other Body Fluids, Arch. Int. Med. **32:**222-225 (Aug.) 1923.

33. Addis, T.: The Number of Formed Elements in the Urinary Sediment of Normal Individuals, J. Clin. Investigation **2:**409-415 (June) 1926.

33a. Patients M. B., C. B. and S. P. were reexamined in March, February, and March of 1940 respectively. The findings were the same as those noted in 1939.

CASE 2.—*Popliteal abscess, moderately severe nephritis, recovery.*

D. T., a 10 year old Negro boy, was admitted to the surgical service on April 12, 1936, with cellulitis of the left leg, a condition which had appeared earlier in the day following a superficial scratch. Hot compresses were applied, and on April 17 an abscess in the left popliteal region was incised; no cultures were made. The patient's temperature fell from an initial 104 F. (40 C.) but never became quite normal; he was sent home on April 22. The urine contained no albumin or formed elements on examination April 12 and 22; the blood pressure was not recorded. On April 28 a headache began, followed by vomiting and puffiness of the face. The patient was admitted to the medical service April 30, with a temperature of 104.4 F. and a blood pressure of 128 systolic and 98 diastolic. There was slight puffiness of the face, and the tonsils were enlarged. The operative wound in the left leg had almost healed. The patient was found to have congenital syphilis. The white blood cell count was 8,700. There was albuminuria (3 plus), and the sediment showed 4 to 6 red cells and 5 white cells, with hyaline and granular casts. The nonprotein nitrogen content of the blood was 41 mg. per hundred cubic centimeters, the phenolsulfonphthalein excretion was 70 per cent and the urea clearance 35 to 37 per cent of the normal standard. A culture from the healing abscess showed beta streptococci only. Cultures of material from the throat showed beta streptococci persistently before and after tonsillectomy, performed May 21. (Culture of the tonsillar tissue removed at operation revealed beta streptococci and minute beta streptococci.) After admission the patient's temperature fell to normal in twenty-four hours, the facial edema disappeared, and the wound in the leg healed. The blood pressure was normal after May 7. Several carious deciduous teeth were extracted during his stay. On May 19 the urea clearance was 80 per cent of the normal standard. The urine cleared rapidly. On June 5 an Addis count was normal save for 9,000 casts; the patient's nephritis was regarded as healed, and he was discharged. In March and November 1937 the urine on examination showed no albumin or formed elements, despite the fact that at the time of the November examination the patient had an abscess on his foot from which beta streptococci were isolated.

CASE 3.—*Impetigo, severe nephritis, recovery.*

B. D., an 11 year old Negro girl, whose tonsils had been removed at the age of 5 years, gave the history of having had impetigo on her legs at intervals for several years. Two months before admission crusts appeared on her forehead; on June 18, 1937 generalized edema was noted accompanied by slight soreness of the throat and vomiting. On admission to the hospital, June 25, her temperature was normal and her blood pressure 192 systolic and 96 diastolic. There were a few impetiginous lesions on the head and on one shin. There was generalized edema. A few tonsillar tags remained. The heart was moderately enlarged, and the venous pressure was 215 mm. of saline solution. On June 28 the patient had several generalized convulsions, and rales appeared at the bases of the lungs. The white blood cell count was 5,000. The specific gravity of the urine was 1.007, and there were approximately 4.5 Gm. of albumin per liter. The urinary sediment showed 15 to 20 red cells and 5 to 8 white cells, with hyaline, granular and cellular casts. The nonprotein nitrogen content of the blood was 128 mg per hundred cubic centimeters; the phenolsulfonphthalein excretion was 70 per cent and the urea clearance 35 to 51 per cent of the normal standard. Cultures of material from the cutaneous lesions showed 80 per cent beta streptococci and 20 per cent Staphylococcus aureus. No beta streptococci could be cultured from material from the throat on admission, although they were isolated later during her stay.

After the convulsions, digitalis was administered and a lumbar puncture performed; subsequently improvement was rapid. The edema had disappeared by July 5. Because of the streptococcic cutaneous infection the patient was given sulfanilamide, 2.4 Gm. daily, from June 28 to July 3; the impetigo healed slowly and by August 17, the day of discharge, had disappeared. After July 2 the blood pressure was normal. The urea clearance on June 22 was 85 to 88 per cent of the normal maximum. Although the albuminuria cleared rapidly, microscopic hematuria persisted. There was no accentuation during an attack of acute salpingitis in September. An Addis count on the urinary sediment in June 1938 was normal save for 61 mg. of protein, and the nephritis was regarded as healed. The patient has not been examined since.

CASE 4.—*Pyoderma, severe nephritis, recovery.*

L. G., a 13 year old white girl, who had had scarlet fever and a tonsillectomy at the age of 8, without known complications, acquired, six weeks prior to admission, dermatitis venenata, probably due to sumach; practically the whole body was involved, and some of the lesions became infected. Since the fourth week before admission there had been fever, generalized edema, headache, vomiting and hematuria. On admission Sept. 8, 1937, the patient's temperature was 100 F. (37.8 C.), and the blood pressure was 150 systolic and 105 diastolic. She was pale; her face was puffy, and she had depigmented scars of a healed pyoderma on the extremities and retinal edema and hemorrhages. The tonsillar fossae showed a few tags. The hemoglobin content was 50 per cent, and the white blood cell count was 6,600. The specific gravity of the urine, which was grossly bloody, was 1.015, with albumin (3 plus) and casts of all types. The nonprotein nitrogen content of the blood was 62 mg. per hundred cubic centimeters; the phenolsulfonphthalein excretion was 32 per cent and the urea clearance 18 to 24 per cent of the normal standard. Cultures of material from the throat revealed beta streptococci inconstantly. The patient was given one transfusion. She improved rapidly. Her facial edema disappeared, and the hemoglobin rose. The blood pressure was normal on September 29. On October 14 the urea clearance was 63 to 67 per cent of the normal standard, and the phenolsulfonphthalein excretion on October 18 was 66 per cent. However, when the patient left, October 20, against advice, her urine still showed albumin (1 plus) and numerous red blood cells. In May 1939 her health was good, and her urine showed only a faint trace of albumin and no red blood cells or casts. Her nephritis was regarded as probably healed.

CASE 5.—*Paronychia, moderately severe nephritis, recovery.*

D. G., a 15 year old white girl, who had had sore throat frequently, until a tonsillectomy was performed, at the age of 12, was admitted to the hospital on Dec. 29, 1933. Two weeks previously an infection had appeared on the distal phalanx of her left thumb; five days before admission there were generalized edema, headache and anorexia; two days before admission the finger was opened surgically. On admission the patient's temperature was 100.8 F., and the blood pressure was 160 systolic and 100 diastolic. There were marked generalized edema, small tonsillar tags, and several carious teeth (subsequently extracted on February 6). There was a granulating paronychia on the left thumb, and the terminal phalanx was red and swollen. The retinas were essentially normal. The hemoglobin content was 68 per cent, and the white blood cell count was 13,000. The specific gravity of the urine was 1.010; it contained albumin (1 plus), 20 to 30 red blood cells and 3 leukocytes, with hyaline, granular and red blood cell casts. The nonprotein nitrogen content of the blood was 30 mg. per hundred cubic centimeters;

the phenolsulfonphthalein excretion was 75 per cent and the urea clearance 46 to 49 per cent of the normal maximum. Cultures of material from the throat on December 30, and Jan. 1, 1934 showed a very few colonies of beta streptococci; thereafter, the cultures were constantly negative for that organism. Cultures of material from the site of the paronychia showed beta streptococci, minute beta streptococci and Staphylococcus albus. The patient improved rapidly. The blood pressure reached normal on January 6 and remained normal. By January 11 the edema had disappeared. By January 18 the urinary elements had entirely cleared. By January 30 the thumb had healed. An Addis count on discharge, February 23, was normal save for 900,000 red blood cells, and the urea clearance was 54 to 62 per cent of the normal maximum. In December 1935, because of recurrences of sore throat, the patient was readmitted, and a tonsillectomy was performed; no beta streptococci appeared in cultures of the tissue removed at operation. The patient's urine, which had shown a trace of albumin inconstantly during the interval, was normal, and the urea clearance was 68 to 78 per cent of the normal maximum. Her nephritis was regarded as healed.

CASE 6.—*Pyoderma, severe nephritis, recovery.*

C. B., a 25 year old white man, was admitted to the hospital on Jan. 30, 1933. In 1925 he had had a tonsillectomy; at that time his blood pressure was 110 systolic and 80 diastolic, and his urine was normal as to albumin and sediment. Eight months before admission he and other members of his family suffered an itching eruption of the skin; in his case the eruption soon became covered with crusts. On Dec. 27, 1932, he was seen in the dermatology clinic, and his condition was diagnosed as coccogenous dermatitis and abdominal cellulitis, probably complicating scabies. He was treated with sulfur ointment. Seven days before admission the patient noted dyspnea, vomiting, generalized edema, oliguria and hematuria. On admission the temperature was 101.4 F. and the blood pressure 205 systolic and 130 diastolic. There were generalized edema, a pyoderma of the extremities with crusts and healing lesions, mild pulmonary edema and retinal edema, with one retinal hemorrhage. The tonsils had been cleanly removed. The white blood cell count was 10,800. The urine was grossly bloody, had a specific gravity of 1.020, and showed approximately 6 Gm. of albumin per liter and numerous casts, including red blood cell casts. The nonprotein nitrogen content of the blood was 50 mg. per hundred cubic centimeters; the phenolsulfonphthalein excretion was 45 per cent and the urea clearance 40 to 41 per cent of the normal standard. Cultures of the skin revealed an almost pure growth of beta streptococci with a few colonies of Staphylococcus aureus. Cultures of material from the throat showed small numbers of beta streptococci persistently. Digitalis U. S. P. was administered, and the cutaneous lesions were treated locally. There was rapid improvement; the temperature soon fell to normal, and by Feb. 8, 1933 the edema had disappeared. The blood pressure fell, reaching 130 systolic and 90 diastolic by February 23; it never remained consistently below that level. By March 25 the cutaneous lesions had healed. The urine cleared only slowly and showed red cells on the patient's discharge from the hospital, May 16. The urea clearance had risen to 58 per cent of the normal standard and the phenolsulfonphthalein excretion to 77 per cent. The urea clearance was 97 to 103 per cent of the normal standard in January 1934, and the Addis count was normal save for 45 mg. of protein per hundred cubic centimeters. The nephritis was considered healed. In May 1939, when the patient was last seen, his blood pressure as observed at a single examination was 140 systolic and 100 diastolic, and his urine was normal. He was recovering from a drinking bout at the time and appeared agitated by the examination.[33a]

CASE 7.—*Axillary abscess, moderately severe nephritis, recovery.*

H. M., a 31 year old Negro, had transient lymphangitis of the left arm immediately following cutting of a finger on March 2, 1929. On March 10 he noticed a mass in the left anterior axilla, and on March 12 an axillary abscess was incised and drained in the outpatient department; the pus was not cultured. On March 13 generalized edema developed and subsequently headache, cough and dyspnea. On admission, March 20, the patient's temperature was normal and the blood pressure 150 systolic and 100 diastolic. There was generalized edema. The injured finger was healed and the left axillary abscess nearly so. The tonsils were enlarged but not reddened. There was one retinal hemorrhage. There was a rectal fistula. The white blood cell count was 11,100. The specific gravity of the urine was 1.010. There was albuminuria (2 plus). In the sediment there were 2 to 3 red cells, 6 to 8 white cells, and many casts, including the cellular variety. The nonprotein nitrogen content of the blood was 30 mg. per hundred cubic centimeters, and the phenolsulfonphthalein excretion was 50 per cent. Cultures of material from the healing abscess showed beta streptococci (1 plus) and hemolytic Staph. aureus (2 plus). Cultures of material from the throat occasionally revealed beta streptococci. (In October 1931, after tonsillectomy, culture of the removed tissue showed no beta streptococci.) The patient rapidly improved after admission. By March 31 the abscess had entirely healed; the rectal fistula persisted. By April 1, 1929, the edema had disappeared and after April 2 the blood pressure was normal. The phenolsulfonphthalein excretion on May 27 was 60 per cent. On discharge, June 21, there was still a trace of albumin as well as a few red cells in the urine. These, too, finally disappeared; in October 1931, the Addis count was normal save for 31,900 casts, and the urea clearance was 80 per cent of the normal maximum. His nephritis was regarded as healed. The patient was last seen in February 1936, when the urine showed a faint trace of albumin and no red cells or casts.

CASE 8.—*Erysipelas, severe nephritis, recovery.*

J. D., a 32 year old Negro, was stricken on Dec. 26, 1932 with a typical attack of erysipelas involving the face. On admission to another hospital, December 31, his temperature was 102.6 F. He was treated with "erysipelas antitoxin" and made a rapid recovery. A specimen of urine examined on Jan 1, 1933 showed no albumin, while one obtained on January 6 contained a trace; neither specimen showed red cells or casts. He was discharged from the hospital on January 7. On January 12 he noticed edema of his legs, and on January 18 he was admitted to the Johns Hopkins Hospital. At this time his temperature was normal, and the blood pressure 190 systolic and 130 diastolic. The cutaneous lesion had healed; however, there were edema of the legs, moderate dilatation of the heart and hemorrhages and exudates in the eyegrounds. The tonsils were not enlarged. The white blood cell count was 5,800. The urine showed a specific gravity of 1.017, albumin (1 plus), 25 to 35 red cells and 4 white cells, with many hyaline, granular and red cell casts. The nonprotein nitrogen content of the blood was 30 mg. per hundred cubic centimeters; the phenosulfonphthalein excretion was 65 per cent and the urea clearance 38 to 42 per cent of the normal maximum. Beta streptococci could not be isolated from the throat. The Wassermann reaction of the blood was positive, and the patient had a history of inadequately treated syphilis. He made a rapid recovery. The blood pressure reached normal levels on January 26, and by January 29 the edema had disappeared. On March 7 the urea clearance was 90 to 92 per cent of the normal standard. The urine contained no albumin after the second day of the patient's stay in the hospital but continued to show red cells

when he was discharged as asymptomatic on April 5, 1933. In April 1934 he survived bacteremia caused by Salmonella suipestifer, with no evidence of any renal disease during its course. An Addis count of the urinary sediment in May 1934 was normal save for a slight increase in the protein to 40 mg. His nephritis was considered healed. The patient was last seen in May 1939, when his urine was normal.

CASE 9.—*Pyoderma, severe nephritis, recovery.*

C. McK., a 60 year old Negro, was first seen in the outpatient department in 1935 with the complaint of dyspnea. He was markedly obese; his blood pressure was 120 systolic and 90 diastolic, and his heart was normal. His urine showed no albumin. In 1936 ulcers appeared on the lower part of his right leg and were persistent. Three weeks before admission the area involved by these ulcers became edematous. Two weeks before admission he had a head cold and slight soreness of the throat lasting one day. Six days before admission he noticed turbidity of the urine, headache, increased dyspnea with cough and, finally, edema of the ankles. On admission, Feb. 25, 1938, his temperature was 101 F. and his blood pressure 210 systolic and 140 diastolic. He was markedly obese and moderately orthopneic, with a nonproductive cough. There was pitting edema over the legs. The tonsils were small. On the right shin there was a 15 cm. band of healing and crusted shallow ulcerations. There was arteriovenous compression of the retinal vessels, although the peripheral vessels were not sclerosed. The heart was moderately enlarged. The venous pressure was 215 mm. of saline solution. The white blood cell count was 6,100. The urine had a specific gravity of 1.026; it showed approximately 2 Gm. of albumin per liter, 90 red blood cells and 15 white blood cells, with hyaline, granular and red blood cell casts. The Wassermann reaction of the blood was positive. The nonprotein nitrogen content of the blood was 32 mg. per hundred cubic centimeters; the phenolsulfonphthalein excretion was 61 per cent and the urea clearance 60 per cent of the normal standard. Beta streptococci were isolated from the lesions on the leg in pure culture; none were observed in cultures of material from the throat. The patient was given digitalis, and sulfanilamide, 3.6 Gm. daily, from February 28 to March 8. There was rapid improvement. The blood pressure reached normal on March 8 and remained so. By March 18 the ulcers had healed, and by March 25 the edema had disappeared. On the patient's discharge, April 26, the urea clearance had risen to 85 and 110 per cent of the normal standard, and the urine showed only a few red blood cells and a trace of albumin. In August the ulcers reappeared on his leg, at the same site; only Bacillus coli could be isolated from them. There was no flare-up in the nephritis. In May 1939 the ulcers had healed, the urine was normal for the first time, and the nephritis was considered healed.

CASE 10.—*Erysipelas, mild nephritis, recovery.*

S. P., a 45 year old white woman, noted the onset of an attack of erysipelas of the face on Nov. 11, 1933. The lesion spread, and the patient began to vomit. On her admission to the hospital, November 15, the disease being of four days' duration, her temperature was 100 F. and her blood pressure 120 systolic and 60 diastolic. There was considerable involvement of the face by the erysipelas, and the patient seemed lethargic. There was no edema, save of the face. The tonsils were not enlarged. The white blood cell count was 11,400. The urine was grossly bloody, had a specific gravity of 1.010, and showed albumin (2 plus) and many granular casts. The nonprotein nitrogen content of the blood was 66 mg.; the phenolsulfonphthalein excretion was 30 per cent and the urea clearance 21 per

cent of the normal standard. No cultures of skin were made; cultures of material from the throat showed beta streptococci inconstantly. By November 23 the erysipelas had healed, and thereafter the patient was asymptomatic. By December 5 the nonprotein nitrogen content of the blood had fallen to 36 mg. per hundred cubic centimeters. Four periapically infected teeth were removed. On her discharge, Jan. 24, 1934, the phenolsulfonphthalein excretion was 65 per cent but the urea clearance only 42 to 48 per cent of the normal standard. Although the gross hematuria subsided twenty-four hours after her admission, the patient showed microscopic hematuria during her entire stay. By March 1934 her urine showed no albumin or red blood cells; her nephritis was regarded as healed. In June 1938 her blood pressure, which had always been normal, was discovered to be 175 systolic and 100 diastolic, and there was a faint trace of albumin in the urine; she complained of menopausal symptoms. In May 1939 the menopausal symptoms were still present. Her blood pressure was very labile, varying from 155 systolic and 98 diastolic to 195 systolic and 120 diastolic during a two days' stay in the hospital. The urea clearance was 48 to 64 per cent of the normal maximum, and an Addis count was normal save for 55 mg. of protein.[33b]

CASE 11.—*Pyoderma, severe nephritis, becoming quiescent.*

T. McK., a 33 year old white man with a history of alcoholism, had had furuncles on his buttocks since March 1932. For eight months previous to his admission to the medical service he had had chronic dermatitis on his left forearm; the disease had started as a "boil." Since Christmas 1933 he had had edema of the face and ankles. In January 1934 his blood pressure was 196 systolic and 126 diastolic, and albuminuria and microscopic hematuria were noted. The edema persisted, and he was admitted to the medical service on March 13. His temperature on admission was normal and his blood pressure 152 systolic and 94 diastolic. There was slight edema of the ankles, together with general bogginess of the tissues. On the flexor surface of the left forearm there was a circumscribed, elevated and crusted reddish eruption, measuring 5 by 2.5 cm. The tonsils were not enlarged. There was a pilonidal sinus (removed on April 25). The white blood cell count was 8,100. The urine showed a specific gravity of 1.010, and contained approximately 0.2 Gm. of albumin per liter. In the sediment there were 30 to 40 red blood cells and 10 white blood cells, with hyaline, granular and red blood cell casts. The nonprotein nitrogen content of the blood was 34 mg. per hundred cubic centimeters; the phenolsulfonphthalein excretion was 48 per cent and the urea clearance 60 to 65 per cent of the normal standard. These levels persisted during the patient's stay, as did the urinary elements and the hypertension. Beta streptococci were repeatedly isolated from the lesion on the arm, which did not respond to hot compresses and ultraviolet ray therapy. On May 26 the area of dermatitis was excised and the site successfully grafted with skin. The skin removed at operation revealed numerous abscesses about the hair follicles, and cultures of the specimen showed beta streptococci with a predominance of Staph. aureus. Beta streptococci were not found in cultures of material from the throat, the furuncles on the buttocks or the pilonidal sinus. On discharge, June 23, the patient's condition was essentially unchanged from that on admission. In April 1935, although he was asymptomatic, his blood pressure was 155 systolic and 100 diastolic, and there was marked albuminuria as well as microscopic hematuria, with the renal functional tests giving the same results as previously. The nephritis was classified as chronic, and the prognosis seemed gloomy. However, when the patient was next seen, in June 1939, he appeared healthy, and there was no infection of the skin. The highest blood pressure obtained during his three days' stay in the

hospital was 135 systolic and 90 diastolic. An Addis count showed 1,108 mg. of protein, 352,000 red blood cells, 704,000 leukocytes and 110,000 casts; 88 per cent of the latter were of the hyaline variety and the rest granular. The phenolsulfonphthalein excretion was 59 per cent and the urea clearance 78 to 86 per cent of the normal maximum. With the presence of albumin and casts in the urine as the only evidence of renal abnormality, the patient's nephritis was classified as quiescent; in the course of the four years since he was last seen, there had been definite regression of the signs of renal damage.

RECAPITULATION OF THE CASES PRESENTED (TABLE 2)

Incidence of Type of Nephritis.—Infected wounds and infections of the skin preceded the onset of symptoms in 11 of the 153 patients with type A glomerular nephritis (group 1), or in 7.2 per cent. Type A nephritis of Longcope [29] is that which follows an acute infection. In 4 of the patients (B.D., C.B., C.McK. andT.McK.) the infection of the skin had existed for a relatively long period, varying from two to twenty-four months, before the onset of symptoms of renal disease; the infections can therefore hardly be called "acute." However, since the nephritis which followed them had the sudden onset and other characteristics of type A, rather than those of type B, in which the onset is insidious and the outcome usually very unfavorable, I have classed the 4 patients in question along with the other 7 in group 1. Four of the patients had pyodermas, 2 infections following wounds, 1 a paronychia, 2 impetigo and 2 erysipelas. It should be noted that in the few days preceding their admission to the hospital, 2 patients (M.B. and C.McK.) had mild sore throat; the relationship of pharyngeal foci of infection to the nephritis is discussed in the paragraph on the bacteria present.

Age of the Patients.—The age of the 11 patients varied from 9 to 60 years; 6 of them were 25 years or older. Since patients under 12 years of age are only rarely admitted to the adult medical service, our series is unduly weighted in favor of the older age groups.

Bacteria Present.—For 4 of the patients no cultures of the cutaneous lesions were made. Two of the 4 (J.D. and S.P.) had erysipelas; the pyoderma of a third (L.G.) had completely healed before admission. Of the remaining 7 patients, beta hemolytic streptococci were obtained in pure culture from the skin of 2 and these organisms in association with staphylococci from the skin of 5. Although none of the patients had a severe sore throat before the onset of nephritis, 2 of them (M.B. and C.McK.) did have mild pharyngitis in the few days before admission; the tonsils of M.B. were enlarged and red on admission, and from them beta streptococci were cultured. With the exception of this infection in M.B., there was no evidence that acute pharyngitis contributed to the onset of nephritis, but in the cases of 4 of the patients (M.B., D.T., D.G. and H.M.) it was thought advisable, at one point or another in the course

TABLE 2.—*Summary of Eleven Cases of Glomerular Nephritis Following Cutaneous Infection*

Classification	Name	Age	Sex	Race	Type of Cutaneous Infection	Bacteria Found in Cultures of Infected Skin	Other Foci of Infection with Beta Streptococcus	Prodromal Period	Total Duration of Cutaneous Infection	Duration of Cutaneous Infection After Onset of Nephritis	Duration of Symptoms of Active Nephritis†	Total Duration of Nephritis to "Healing"	Highest Antistreptolysin Titer, Units
Severe and moderately severe, with recovery	M. B.	9	M	W	Impetigo	None	Pharynx	11 days	24 days	13 days	7 days	57 days	500
	D. T.	10	M	N	Abscess following wound	Beta streptococcus	Pharynx	16 days	32 days	16 days	9 days	38 days	250
	B. D.	11	F	N	Impetigo	Beta streptococcus, Staph. aureus	Pharynx	Less than 60 days	Less than 4 months (?)	Less than 60 days (?)	17 days	12 months	200
	L. G.	13	F	N	Pyoderma	None	Pharynx	14 days	42 days	28 days	49 days	20 months	...
	D. G.	15	F	W	Paronychia	Beta streptococcus, minute beta streptococcus, Staph. aureus	Pharynx transiently	9 days	46 days	37 days	18 days	24 months	25
	C. B.	25	M	W	Pyoderma	Beta streptococcus, Staph. aureus	Pharynx	Less than 8 months	10 months	60 days	31 days	12 months	100
	H. M.	31	M	N	Abscess following wound	Beta streptococcus, Staph. aureus	Pharynx	11 days	29 days	18 days	20 days	29 months	...
	J. D.	32	M	N	Erysipelas	None	None	17 days	12 days	Healed before onset	17 days	15 months	500
	C. McK.	60	M	N	Pyoderma	Beta streptococcus	None	Less than 24 months	25 months	27 days	34 days	17 months	250
Mild with recovery	S. P.	45	F	W	Erysipelas	None	Pharynx	? 4 days*	12 days	? 8 days*	21 days‡	4 months	25
Severe, becoming quiescent	T. McK.	38	M	W	Pyoderma	Beta streptococcus, Staph. aureus	None	Less than 6 months	11 months	5 months	More than 16 months	Quiescent	250

* Nephritis was present on admission.
† Edema, hypertension and azotemia were noted.
‡ The nonprotein nitrogen content of the blood was normal by Dec. 6, 1933.

of the disease, to perform tonsillectomy. In addition, the fact that beta hemolytic streptococci were repeatedly isolated from the throats of 7 of the 11 patients justly throws some doubt on the statement that the skin was the only significant focus of infection in these subjects. It has been stated by Long and Bliss [34] that in the winter months 10 to 13 per cent of cultures of material taken from the throats of normal persons in Baltimore show beta hemolytic streptococci. Winkenwerder, McLeod and Baker,[3] in a study of 22 patients who had recovered from glomerular nephritis, including 1 patient from this series of 11 patients, found that 7, or 32 per cent, of the patients had throat cultures positive for beta streptococci after recovery.

Prodromal Period.—In 6 of the patients the prodromal period varied from nine to seventeen days; an additional patient was admitted on the fourth day of erysipelas with signs of nephritis already present. In the remaining 4 patients, relatively chronic dermatitis had been extant for from two months to two years. With regard to the last group, there is, of course, no means of ascertaining whether beta hemolytic streptococci were present in the cutaneous lesions during the whole period of their duration. It is interesting that the patient B.D. had had several attacks of impetigo prior to that complicated by nephritis.

Course of the Nephritis.—None of these infections of the skin seemed to distinguish itself in severity or in any other way from infections of the same category not followed by nephritis. There was no constant story of previous susceptibility to streptococcic infections of other types, such as sore throat. The nephritis itself was typical acute glomerular nephritis of varying severity, with the usual urinary findings in all the patients, hypertension in 9 and evidence of cardiac insufficiency in 3. There was edema in 9 patients, and 3 had marked temporary depression of renal function with nitrogen retention. The disease was classified as severe in 6 patients, moderately severe in 4 and mild in 1.

The disease of 1 patient, T.McK., remained in a quiescent stage. The remaining 10 patients, representing 91 per cent of our very small series, recovered. (Longcope [2a] in 1938 estimated that complete recovery occurred in 55 to 65 per cent of all the patients with nephritis of type A.) Within seven weeks after the onset of symptoms of nephritis, 10 of the 11 patients had become asymptomatic and were well except for the persistence of mild albuminuria and hematuria; in 7 of the patients the signs of renal disease, other than the urinary ones, were of less than three weeks' duration. The total duration of the nephritis from the time of

34. Long, P. H., and Bliss, E. A.: Studies upon Minute Hemolytic Streptococci: IV. Further Observations upon the Distribution of Ordinary and Minute Beta Hemolytic Streptococci in Normal and Diseased Human Beings, J. Infect. Dis. **62**:52-57 (Jan.-Feb.) 1938.

onset to the time at which the process was classified as completely healed was less than six months in 3 patients, twelve months in 2, twenty-four months in 4 and twenty-nine months in 1. Three patients (J.D., H.M. and S.P.) showed a faint trace of urinary albumin irregularly on dispensary visits following the date on which they had been classified as "recovered." Two additional patients (B.D. and L.G.), had a very faint trace of albumin in the urine when last seen, but since their disease was of relatively recent origin and improvement had been progressive, they have been classified as "recovered" for the purposes of this paper. In 2 patients classified as "recovered," an elevation in the previously normal blood pressure was noted on examination five years after the acute stage of the nephritis. One of these patients (S.P.) was passing through the menopause; the blood pressure of the other patient (C.B.) was determined only once, at a time when he was obviously mentally perturbed.

COMMENT

Earlier in the paper I stated that it was hoped that a study of these cases of nephritis following infections of the skin might throw light on the relationship of a persistent focus of infection to the evolution of chronic nephritis. Two factors tend to vitiate any pertinent conclusions which might be drawn—first, the brevity of the series and, second, the fact that beta hemolytic streptococci were persistently isolated from another focus than the skin, the pharynx, in 7 of the 11 patients. I can point to only one observation as possibly bearing on the role of persistence of infection in promoting pathologic activity. The only patient who has not recovered (T.McK., whose nephritis is now in the quiescent stage) represents the 1 patient of the 11 patients whose cutaneous infection persisted for longer than two months after the onset of nephritis; his infection was present for five months after he first noted edema (table 2). Although the only demonstrable focus of hemolytic streptococci, an area of localized dermatitis on his arm, was finally excised surgically and the denuded area sucessfully grafted with skin, his nephritis has never completely healed. The fact that his urine still contains albumin and casts five years after removal of the focus of streptococcic infection suggests that irreparable damage to the kidneys had been done previous to excision of the infected skin.

Before concluding, it should be noted that a study of table 2 bears out the well known fact that the process of healing of the renal lesions of glomerular nephritis entails a period of several months. Slight albuminuria or microscopic hematuria outlasted the lesion of the skin by one to two years in 7 of the 10 patients whose nephritis finally healed.

SUMMARY

The literature on the occurrence of glomerular nephritis following infections of the skin has been reviewed.

The protocols of 11 patients in whom acute and often severe hemorrhagic nephritis followed infected wounds and infections of the skin have been presented, with comments.

Beta hemolytic streptococci were isolated from the cutaneous lesions of 7 of the 11 patients, twice in pure culture and five times in association with staphylococci. Two of the 4 patients for whom no cultures of the skin were made had erysipelas.

The nephritis is believed to have healed in 10 of the 11 patients and to have become quiescent in 1 patient. The single patient whose urine still shows significant abnormalities is the only one in whom the infection of the skin did not heal within two months after the onset of symptoms of nephritis.

BLOOD

REVIEW OF RECENT LITERATURE

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The trend in hematology in 1939 was toward the experimental and chemical aspects of the physiology and pathology of the blood and of the blood-forming organs. Studies of material obtained by aspiration of sternal marrow have become an integral part of the analysis of disease. The present review contains data from selected articles published in 1939, with a few from previous years. With the growth of the literature on blood, the number of articles published has increased to such an extent that it has been necessary to omit some publications which no doubt contain material of interest and value. Some of these will be abstracted in later reviews.

PERNICIOUS ANEMIA

A most scholarly consideration of the more important facts and theories concerning knowledge of the etiologic factors in pernicious anemia is given by Meulengracht.[1] His presentation deserves a thoughtful perusal by all physicians who are interested in following the remarkable recent development of new information dealing with the etiology of the disease. It is his belief that sufficient data are available to picture the normal process which controls the development of the erythrocytes as follows: (1) the extrinsic factor is supplied by the food; (2) the intrinsic factor is produced by the pyloric glands, that is, glands located in the pylorus, in the duodenum and to a lesser extent in the cardiac

From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan.

1. Meulengracht, E.: Histologic Investigations into Pyloric Gland Organ in Pernicious Anemia, Nord. med. (Hospitalstid.) **1**:11, 1939; Histologic Investigation into Pyloric Gland Organ (and Brunner's Glands), Am. J. M. Sc. **197**:201, 1939; Etiological Factors in Pernicious Anemia, in a Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p. 72.

region of the stomach; (3) an interaction between these two factors occurs in the small intestine, whereby the ultimate principle is elaborated; (4) this principle is then absorbed from the small intestine, especially from the ileum; (5) this principle is then carried by the blood to the liver and other organs, where (6) it is stored for further use.

On the basis of the familial incidence of pernicious anemia, the prevalence of achlorhydria in blood relatives and the fact that the achylia precedes the development of pernicious anemia by ten years, twenty years or longer, he expresses the belief that there is a hereditary defect in the stomach which is transmitted from one generation to another. A review of his own fundamental work is given, which indicates that the intrinsic factor is the product of the pyloric glands in the stomach and of Brunner's glands in the duodenum. These he designates as the pyloric gland system, as distinguished from the glands of the fundus, which secrete hydrochloric acid, pepsin and rennin. The author emphasizes, however, that one finding when first considered does not appear to be in accord with his theory. It does not introduce, however, an insurmountable difficulty to the acceptance of it. It is the fact that when the stomachs of patients with pernicious anemia are examined the histologic picture is just the reverse of what one would anticipate. In other words, anatomic studies show that the pyloric glands, which produce the intrinsic factor, are normal and that the abnormalities involve the glands of the fundus. Two suggestions are made to reconcile this fact with his theory: (1) The glands of the fundus may act as a starter, or pacemaker, for the pyloric gland system either through production of hydrochloric acid and pepsin or (perhaps) through a hormonal action or (2) the interaction between the intrinsic and extrinsic factors may occur mainly in the small intestine, where the changes resulting from achlorhydria may render conditions unfavorable for such a process. Both of these explanations are ingenious, logical and worthy of serious attention, but they are still unproved. The author is the first to admit this, in his statement that "there is still much work to be done in this field of investigation."

Another point to which considerable discussion is devoted is the rather confusing but correct information that the intestines have some anti-pernicious-anemia activity. This fact appears to be clearly established. A table taken from the work of the Finnish investigator Votila is given, which shows the relative potency of the various parts of the gastrointestinal tract. The following list is based on the assumed activity of the total stomach as 100:

Cardia	30	Jejunum	24
Fundus	2	Ileum	44
Pylorus	120	Large intestine	9
Duodenum	35		

It is Meulengracht's tentative belief that the anti–pernicious–anemia activity of the intestines is due to the presence of the completed substance, of the liver factor or perhaps of an intermediate product. The observations of Castle support this view. He found that prolonged washing of the ileum removes its hemopoietic activity, which would lead one to consider that the principle is formed elsewhere and is merely absorbed by the intestinal wall rather than secreted by it. Meulengracht has observed also that the intestinal material possesses "a certain degree of thermostability," which would indicate that it is a different substance from the intrinsic factor secreted by the stomach, as the latter is easily destroyed by heat.

Kaufmann and Thiessen [2] studied the blood and the gastric secretions of 48 patients with pernicious anemia and 168 of their blood relatives in order to obtain an idea concerning the familial incidence of the disease and information concerning its mode of transmission. In 8 families, or 16.7 per cent, more than one member was found to have the disease, as follows: "once in twin females, once among three brothers and sisters, twice in mother and son, twice in brothers, once in brother and sister and once in cousins." The authors attribute the high incidence in their studies to (1) the fact that the relatives investigated had all reached the age when pernicious anemia commonly develops and (2) the fact that the hospitals (of Hamburg, Germany) had excellent records, which made it possible to trace the history of deceased relatives. The occurrence of anacidity in 1 parent in each of 3 cases investigated in which both parents were examined led them to conclude that pernicious anemia is transmitted as a dominant characteristic. They also conclude that in families there may be persons who do not have fully developed pernicious anemia but are "carriers" of the disease from a hereditary standpoint. These persons may have glossitis, atrophy of the papillae of the tongue and either anacidity or subacidity. The occurrence of essential hypochromic anemia in relatives of patients with pernicious anemia is observed too often for the association to be fortuitous. As the authors do not believe that the two diseases can have the same extrinsic cause, they conclude that they must have a common, inherited one. In support of this view they state that they have observed a patient with essential hypochromic anemia in whom pernicious anemia developed, which speaks for a pathogenic relation between the two diseases. The authors are in agreement with Castle that pernicious anemia is due to a diminution in secretion of the intrinsic factor, which they believe is an inherited dominant characteristic. It is emphasized, however, that this gastric deficiency can also be purely exogenous in origin but that such an origin is less important.

2. Kaufmann, O., and Thiessen, K.: Hereditary Biology of Pernicious Anemia, Ztschr. f. klin. Med. **136**:474, 1939.

Jahsman [3] reviews the histories of 223 cases of pernicious anemia observed at the Henry Ford Hospital between 1926 and 1938. Some useful suggestions are made concerning therapy, which in his review are summarized under the title "Treatment of Pernicious Anemia." An idea of the incidence of the disease is given by the statement that there was an average of 2.2 cases of pernicious anemia for every thousand new admissions to the hospital during the period. The disease occurred with equal frequency in the two sexes, which is in accord with the current opinions concerning sex distribution. The age range was from 17 to 81 years; most of the patients were aged 40 or over. The interesting observation is made, with which we are in agreement, that there is an increasing number of patients in whom the disease develops while they are in the early thirties or even younger. In this group, for example, between 1926 and 1931, 10 per cent of the patients were under 40 years of age; 3 were under 30, the youngest being 29. In the new cases observed between 1931 and 1938, 18 per cent of the patients were under 40; 10 were under 35, 5 were under 30 and the youngest was 17. This tendency of a disease which is commonly considered to be limited to persons of middle age or older to occur in younger persons appears to obtain with pernicious anemia as well as with other diseases, such as coronary thrombosis. While this observation arouses considerable speculation, the real explanation is not apparent at present.

Davidson [4] presents an admirable summary of the knowledge concerning the factors involved in production of the macrocytic anemias and emphasizes the main types with illustrative case histories. His review merits a careful reading by all workers in the field of hematology; the data are well epitomized, and some engagingly provocative statements are made. He considers that there are many types of macrocytic anemia which have in common only the fact that the average size of the erythrocyte is greater than normal. Otherwise they differ in causation, in response to treatment and in the blood picture. In general, however, they can be divided into two groups.

Group 1 consists of macrocytic anemias developing from megaloblastic bone marrow and consequent on a deficiency of a specific factor essential for the continuation of normal blood formation.

Group 2 consists of all macrocytic anemias which are due to a cause which differs from that mentioned. Such macrocytic anemias are relatively rare and result from widely differing causes. In a majority of cases, however, the macrocytosis is secondary to "prolonged stimulation or irritation of the bone marrow." Macrocytic anemias belonging

3. Jahsman, W. E.: Prevalence of Pernicious Anemia: Review of Two Hundred and Twenty-Three Cases, J. Michigan M. Soc. **38**:405, 1939.

4. Davidson, L. S. P.: The Mechanism of Megaloblastic Blood Formation, Cambridge M. J. **64**:474, 1939.

to group 2 are present: (*a*) with some forms of hemolytic anemia, for example, acholuric jaundice; (*b*) occasionally in cases of malignant malaria and lead poisoning; (*c*) not infrequently in cases of aleukemic leukemia and the terminal stages of leukemia, and (*d*) in cases of Hodgkin's disease and malignant disease with metastasis to the bone marrow.

The macrocytic anemias of group 2 may be differentiated from the true megalocytic anemias on three main grounds: (1) by recognition of the cause; (2) by full examination of the blood picture, which differs in important details in regard to red blood cells, white blood cells and platelets; (3) by failure of the condition to respond to anti-pernicious-anemia medication, and (4) by the favorable effect of other measures, such as splenectomy and irradiation. Davidson aptly remarks that "all megalocytic anemias are macrocytic, but . . . all macrocytic anemias are not megalocytic."

The major portion of Davidson's communication deals primarily with the anemias which arise from megaloblastic blood formation. The mechanism of this is discussed from the standpoint of Castle's hypothesis, with which the author is in agreement. The views of the author regarding the causes of these various anemias may be summarized as follows:

Pernicious anemia develops in patients who are born with stomachs which fail to secrete first hydrochloric acid, then enzymes and finally the intrinsic factor. The name pernicious anemia should be reserved for the megaloblastic anemia which arises from a loss of intrinsic factor in association with a constitutional defect in gastric secretion. The inability of the stomach to secrete hydrochloric acid and the intrinsic factor is permanent and irreversible; hence substitution therapy must be continued for life.

Davidson believes that pernicious anemia of pregnancy develops in a woman who has a latent constitutional factor in the stomach which is made apparent by the increased demands of the mother and the fetus for the antianemia principle. It is likewise consequent on lowering of gastric function, which constantly occurs during pregnancy. Davidson intimates that possibly true pernicious anemia develops in such women twenty to thirty years after recovery from the pernicious anemia of pregnancy.

It is believed that in extremely rare instances macrocytic anemia may arise when there is a temporary loss of the intrinsic factor due to prolonged dietary deficiency and chronic gastritis. The author presents what he considers to be such a case, in which there was a "permanent cure" of the megalocytic anemia, with return of free hydrochloric acid in the gastric secretions and reappearance of the intrinsic factor as proved by the biologic test.

Proof that macrocytic anemia may develop from a lack of the extrinsic factor is to be found in the occasional case in which the condition responds to oral ingestion of autolyzed yeast. While such a deficiency is rare in temperate climates, it is apparently common in the tropics. The characteristic features of tropical anemia are summarized by Davidson as follows: The blood picture is identical with that of true pernicious anemia; the amount of hydrochloric acid in the gastric secretions is usually normal; there is no increase in plasma bilirubin; lesions of the central nervous system never develop, and an excellent response to autolyzed yeast occurs. It is principally for the last reason that tropical macrocytic anemia has been regarded as a deficiency state due to lack of the extrinsic factor.

Megaloblastic blood formation may result from failure of absorption of the specific antianemia factor due to intestinal impermeability, diarrhea or mechanical causes, such as fistulas of the bowel or short-circuiting operations.

Macrocytic anemia may develop in patients with disease of the liver when there is failure of storage or of final synthesis of the antianemia factor in that organ. While this concept is accepted by Davidson, he does not believe that the defect in storage can be solely responsible for the anemia in some cases, because in them there is partial or complete failure to respond to parenteral liver therapy. It is possible in such instances that the liver may play some role in final elaboration of the antianemia product and that this function is injured in patients with disease of the liver. Or, the suggestion is made, the failure to respond may be due to injury to the bone marrow from the toxic products formed or retained as a result of failure of the liver.

Finally, the possibility of development of hyperchromic macrocytic anemia due to failure of the bone marrow to utilize the specific antianemia factor (achresthic anemia) is discussed by Davidson. He likewise considers the possibility that the absence of a favorable response to potent anti-pernicious-anemia therapy may be explained by exhaustion of the bone marrow (aplastic anemia). The final acceptance of the concept of achresthic anemia is held in abeyance, however, pending additional studies.

Schenken, Stasney and Hall [5] report studies which are confirmatory of previous work indicating that the pyloric and prepyloric regions are a source of the "intrinsic factor." An extract was prepared from the liver of a patient whose death was due to carcinoma of the pyloric and prepyloric regions of the stomach. No data, however, are given which

5. Schenken, J. R.; Stasney, J., and Hall, W. K.: Lack of Antianemic Principle in Human Liver from Case of Carcinoma of Stomach, Proc. Soc. Exper. Biol. & Med. **40**:89, 1939.

show that this patient had macrocytic anemia. The liver extract from this patient failed to produce a reticulocyte response, whereas a similar extract prepared from a patient who died from a cerebral hemorrhage was potent.

Brunschwig and his associates [6] postulate that the achlorhydria invariably observed with pernicious anemia may be associated with the formation of some substance which, acting on the foveolar portions of the gastric glands or on the parietal cells themselves, leads to inhibition of the secretion of hydrochloric acid and its liberation as free acid. In order to study this problem, gastric juice obtained from patients with pernicious anemia was injected intravenously into dogs with gastric pouches. The changes in the gastric secretions collected from the pouches were noted after feeding. The authors observed a transitory marked depression of the secretion in the pouch and achlorhydria (89 per cent of the samples) when the gastric juice of 16 of 18 patients with pernicious anemia was injected intravenously. Injection of gastric juice from a group of patients who did not have pernicious anemia caused similar gastric secretory inhibition in only 18 per cent of the tests. It was determined that this secretory depressant effect of gastric juice is abolished by boiling for ten minutes. The authors interpret their observations as suggesting that the gastric secretory depressant found in relatively high concentration in the gastric juice of patients with pernicious anemia represents a marked increase of a factor that may be normally present in relatively low concentrations in the gastric secretions of patients who do not have pernicious anemia.

It is stated by Dexter and his co-workers [7] that previous studies by various workers have demonstrated the effectiveness of preparations from the small intestines and colon of the hog in bringing about an increased production of blood in patients with pernicious anemia. Rather than conclude that this indicates a secretion of the intrinsic factor by the intestines as well as by the stomach, these observers consider that this blood-forming activity may be due entirely to passive adsorption of the intrinsic factor which is formed in the stomach. In support of this view they demonstrated that prolonged washing removed the hemopoietic activity of the lower half of the intestine, whereas a similar procedure had no effect on the stomach. Washing did not remove the activity of the duodenal mucosa, but mincing and then washing rendered it inactive, although similar treatment of stomach tissue

6. Brunschwig, A.; Van Prohaska, J.; Clarke, T. H., and Kandel, E.: A Secretory Depressant in Gastric Juice of Patients with Pernicious Anemia, J. Clin. Investigation **18**:415, 1939.

7. Dexter, S. O.; Heinle, R. W.; Fox, H. J., and Castle, W. B.: Basis of the Hematopoietic Activity in Pernicious Anemia of Desiccated Hog Ileum, J. Clin. Investigation **18**:473, 1939.

did not have the same effect. They demonstrated, furthermore, that the anti-pernicious-anemia effect of ileum is readily destroyed by boiling, which distinguishes it from the active thermostable principle in liver. It is suggested that the hemopoietic ability of the ileum of the hog is due to passive adsorption of gastric secretion. The authors are uncertain whether the activity of the washed duodenum is due to active secretion of the extrinsic factor or to the ineffectiveness of the washing process in eliminating higher local concentration of adsorbed intrinsic factor. These experiments are illuminating, but they are difficult to interpret, as so much depends on the differential effectiveness of "washing" in determining whether a material is secreted or absorbed by a tissue.

Further studies on liver are reported by Dakin and West,[8] who attempt to determine the chemical identity of the active principle controlling the regeneration of blood in patients with pernicious anemia. They have previously shown that there is a substance in liver which has this effect; it is a peptide and in some respects resembles a typical albuminose. Karrer, Frei and Fritzsche[9] report that the active substance is a biuret-negative peptide with an elementary structure which resembles the product isolated by Dakin and West. The present report of the latter two investigators shows that the liver material active in subjects with pernicious anemia is precipitated by typical albuminose precipitants, such as bile, taurocholic acid and nucleic acid. A further fact of additional interest is that the peptide which they have isolated is free from the nicotinic acid group.

Barker and Hummel[10] give a review of the literature and report 2 new cases of macrocytic anemia associated with intestinal strictures and anastomoses. This article is abstracted in considerable detail because it discusses so thoroughly the entire problem regarding the relation of the macrocytic anemias to the intestinal tract and prevents a novel theory concerning the cause of pernicious anemia. They state that the first instance of this association was recorded by Faber[11] in 1895. Since

8. Dakin, H. D., and West, R.: Hematopoietic Substance in Liver, Proc. Soc. Exper. Biol. & Med. **40**:124, 1939.

9. Karrer, P.; Frei, P., and Fritzsche, H.: Ueber einen Bestandtiel von gegen perniziöse Anämie hochaktiven Lebertraten, Helvet. chim. acta **20**:622, 1937. Karrer, P.; Frei, P., and Ringier, B. H.: Bestandteile von gegen perniziöse Anämie hcohaktiven Lebertraten: II. ibid. **21**:314, 1938.

10. Barker, W. H., and Hummel, L. E.: Macrocytic Anemia in Association with Intestinal Strictures and Anastomoses: Review of Literature and Report of Two New Cases, Bull. Johns Hopkins Hosp. **64**:215, 1939.

11. Faber, K.: Pernicious Anemia Due to Intestinal Trouble, Hospitalstid. **3**: 601, 1895; Perniciöse Anämie bei Dünndarmstrikturen, Berl. klin. Wchnschr. **34**: 653, 1897.

then, reviews by Meulengracht [12] in 1929 and by Hurst [13] in 1933 have brought the number of recorded cases up to 39. The authors have collected 10 more cases from the literature and added 2 of their own, thus making a total of 51 cases for consideration.

In almost all such cases the symptoms are predominantly those of partial intestinal obstruction, namely, diarrhea or intermittent diarrhea and constipation, distention, abdominal cramps and, less frequently, nausea and vomiting. Usually there is marked loss of weight secondary to the gastrointestinal disturbances. Barker and Hummel state that the pathologic picture established by them at necropsy, by operation or by roentgen examination consisted of strictures of the large intestine in 7 cases, enteroenterostomy or enterocolostomy openings in 13, gastrojejunocolic fistula in 4 and gastrocolic fistula in 1. The majority of the strictures of the small intestine were located in the ileum, and of these about one half were definitely tuberculous in origin. Certain of the nontuberculous strictures were due to nonspecific terminal ileitis. Anastomosis of various types was the abnormality in about one third of the cases, and this was most frequently either an enteroenterostomy or an enterocolostomy resulting from surgical procedures which had been performed for the relief of intestinal obstruction.

Anemia of the pernicious type was present in all cases, and in some it was severe, as was indicated by a red blood cell count below 1,000,000 per cubic millimeter in 8 instances. Macrocytosis was specifically mentioned in a great majority of cases; a mean corpuscular volume of over 120 cubic microns was not unusual. Forty-seven per cent of the patients had free hydrochloric acid in the gastric juice, and it probably would have been detected in a larger percentage if the analyses had been made after injections of histamine. The presence of free hydrochloric acid in the gastric secretions of course sharply differentiates this type of macrocytic anemia from true pernicious anemia, which is always associated with achlorhydria. The intrinsic factor of Castle was tested for directly in only 2 cases. In 1 it was present, and in the other it was absent. The response to a diet rich in the extrinsic factor was interpreted as indirect evidence of absence of the intrinsic factor in 2 additional cases.

Studies of the ability of the body to absorb fat, dextrose and ascorbic acid were made in a few instances. It was concluded from the somewhat scanty available data that probably defective intestinal absorption alone cannot explain the development of macrocytic anemia in this group of patients. The paucity of the observations prevents definite acceptance

12. Meulengracht, E.: Pernicious Anemia in Intestinal Stricture, Acta med. Scandinav. **72**:231, 1929.

13. Hurst, A. F.: A Case of Addison's Anemia with Subacute Combined Degeneration of the Spinal Cord and Normal Gastric Secretion Following Chronic Obstruction of the Ileum, Guy's Hosp. Rep. **83**:47, 1933.

of this conclusion, but in our opinion such studies are exceedingly important and are worthy of further investigation. The authors concede that their information is inadequate and that only tentative conclusions can be drawn from it. They have not demonstrated conclusively that the patients fail to absorb the erythrocyte-maturing factor.

The patients were divided into four groups, depending on the type of treatment. Group 1 (23 patients) received supportive treatment for the most part, and 22 died; 3 of the patients who were placed on milk diets were temporarily benefited. This suggests to us that the protein of the milk, perhaps acting as the extrinsic factor, was the component responsible for the improvement in these patients. Group 2 included 9 patients who were treated by various surgical procedures; 5 died so soon after the operation that no conclusion could be drawn regarding the effect on the anemia. The 4 who survived showed striking symptomatic and hematologic improvement after operation. In 2 additional cases an ileocolostomy was performed to circumvent strictures of the terminal portion of the ileum. The immediate results were excellent, but sufficient data were not available to determine whether relapses occurred. The authors stress the fact that macrocytic anemia may develop after an anastomosis has been performed to circumvent strictures, which is important from the standpoint of practical therapeutic management. Group 3 was made up of 9 patients who were treated with liver alone. Six of these showed striking improvement, 3 of whom gave satisfactory responses to oral administration of liver preparations. The results observed in these 3 patients lead the authors to conclude that there was no marked disturbance of intestinal absorption in these cases. Group 4 included 10 patients who were unsuccessfully treated by surgical intervention and were then given liver therapy.

The conclusions drawn concerning various types of therapy for "stricture anemia" are as follows: 1. Without surgical or anti-pernicious-anemia therapy, the outlook for improvement is very poor. 2. A high operative mortality is associated with the surgical procedures employed to correct the intestinal abnormalities. 3. Elimination of the abnormal intestinal condition may or may not be followed by complete cure. 4. An anastomotic operation designed to circumvent a stricture is less likely to succeed than is resection of a stricture or restoration of the normal continuity of the bowel when an anastomosis is the offending lesion. 5. Although liver therapy may control the anemia, it cannot be expected to relieve the symptoms due to partial intestinal obstruction. 6. Surgical treatment is indicated for all patients with strictures and for young patients with anastomoses. 7. Liver therapy alone is indicated for older patients with well functioning anastomoses in whose cases the operative risk is great.

The authors do not believe that the condition of their patients represents a coincidental association of an intestinal lesion with addisonian pernicious anemia. This is because in a number of cases free hydrochloric acid was present in the gastric secretions, in a few there was evidence that the intrinsic factor of Castle was present in the gastric secretion and, finally, surgical correction of the lesion was followed by disappearance of the macrocytic anemia. Among other mechanisms which may have caused the macrocytic anemia is deficient absorption of the hemopoietic principle, such as occurs in cases of sprue. It is conceivable that enteritis due to stagnation occurring above strictures or in short-circuited loops may interfere with absorption of this substance. Evidence against this is furnished by data indicating that in some cases absorption of dextrose, fat and the active principle of liver was unimpaired. In some patients a deficiency of the extrinsic factor in the diet may play an etiologic role; if this is true, it is probably of secondary importance. It is not considered that extensive damage to the liver was important in the causation of anemia in these cases.

According to the authors, this leaves for consideration the possibility that excessive bacterial activity in the intestinal tract may have been the cause of the macrocytic anemia. Such a pathologic change could act (1) by preventing formation of the hemopoietic factor or destroying it or (2) by elaboration of an excessive amount of the "toxic products of bacterial putrefaction," which cannot be neutralized by the detoxifying mechanisms of the body.

Faber, in 1895, was the first to ascribe the macrocytic anemia associated with stricture of the small bowel to absorption of a toxin from the stagnant intestinal contents. Meulengracht in 1921 stated that such an anemia is probably due to absorption of "hematoxic substances" from the dilated and infected portion of the bowel above the stricture. Furthermore, in his opinion such a condition supports the theory of the intestinal origin of cryptogenic pernicious anemia. The experimental production of intestinal stricture in dogs, the treatment of "idiopathic" pernicious anemia by ileostomy and colonic irrigations and the study of pathologic flora in the gastrointestinal tract have all furnished suggestive evidence favoring the enterotoxic theory of pernicious anemia.

Even with the acceptance of Castle's work, which indicates that pernicious anemia is a deficiency disease or at least a "conditioned deficiency state," the authors maintain that the action of the liver principle is still far from clear. They suggest that there is evidence to support the contention that the liver principle may be necessary to promote proper detoxification of some chemical compound or compounds which, if unneutralized, might give rise to a variety of harmful changes through-

out the body. On this basis it may be assumed that the beneficial effects of liver therapy may be due to the ability of the liver principle to detoxify the excess of toxins absorbed from stagnating intestinal contents in subjects with strictures or anastomoses of the small intestine. If this hypothesis were applied to the development of addisonian pernicious anemia, it would be assumed that there is a failure of the body to synthesize the detoxifying principle in sufficient amounts to neutralize the toxic substance normally absorbed from the intestinal tract when stagnation is not necessarily a factor.

We have been interested for a number of years in the mechanism of production of macrocytic anemias associated with abnormalities of the small intestine. It appears to be clearly established that there is a causal relation and that the final proved explanation will provide important new information regarding the causation of the macrocytic anemias. Superficially, it is logical to assume that the anemias associated with intestinal anastomoses are due to a failure in normal absorption of the active principle of liver, although Barker and Hummel appear to have accumulated some evidence against such an interpretation. The theory which has a bearing on the cause of the macrocytic anemia associated with intestinal strictures, although it may not be ultimately substantiated, is a rational one which should provoke further promising etiologic studies.

Alsted [14] is in agreement with Castle and his collaborators that true addisonian pernicious anemia is due to a lack of "intrinsic factor," which is derived from the stomach. There is less adequate evidence, however, to prove that a similar condition can result exclusively from a lack of the "extrinsic factor" in the diet. We are in accord with the statement that in temperate climates cases of such a condition appear to be extremely rare; on the other hand, it is said that they occur more frequently in the tropics. A statement which seems applicable to the theories regarding the cause of the tropical macrocytic anemias is that "in the tropics . . . . conditions are difficult to gauge; it is often impossible to detect the single dietary deficiency causing anemia, and, furthermore, various infections may influence the aspect of the blood." Alsted reports 1 case of macrocytic anemia, stating that many facts make it highly likely that the anemia was due to a deficiency exclusively of the extrinsic factor in the food.

The patient, a man aged 43, had severe anemia (red blood cell count, 1,300,000 per cubic millimeter); a high color index, pronounced glossitis, the characteristic picture of pernicious anemia on sternal puncture and the classic Price-Jones distribution curve were present. Against the diagnosis were a normal icteric index and the presence of free acid in

14. Alsted, G.: Exogenous Pernicious Anemia, Am. J. M. Sc. **197**:741, 1939.

the gastric secretions. We note with interest, however, the complete absence of acroparesthesia, which in our experience is present in 90 per cent of patients with true addisonian anemia. Thorough examination failed to disclose evidence of idiopathic steatorrhea, intestinal stricture, intestinal parasites, pellagra, syphilis, tuberculosis, chronic nephritis, Hodgkin's disease or any other of the diseases that are occasionally accompanied with macrocytic anemia. No specific mention is made, however, of the possibility of extensive disease of the liver or of the employment of tests of hepatic function. Some believe that macrocytic anemia can result from a pathologic change in this organ.

The patient had been on a restricted diet for seven or eight years, which was deficient in meat, eggs and milk. The author regards these substances as the chief sources of the "extrinsic factor." A minute dietary history disclosed that there was no deficiency of the known vitamins, although there was a lowered intake of calcium and phosphorus. According to the author, conclusive evidence of the lack of "extrinsic factor" was obtained when a complete remission, including a reticulocyte response, followed "treatment with nothing but 'extrinsic factor' and plenty of ordinary food." The patient remained well seven months later despite the fact that he did not take any medicine, merely continuing to consume a well balanced diet. It is of interest that there was complete restoration of the gastric secretion to normal. The suggestion is offered that a deficiency of the "extrinsic factor" causes achylia and that this in turn results in impaired absorption of the already scantily available extrinsic factor and of the eventually formed antianemia factor. The author concludes with the interesting speculative statement that "exogenous pernicious anemia" occurs more frequently than is generally believed. Its presence is obscured, however, because liver and stomach preparations are equally effective for the exogenous and the endogenous form.

The studies of Wintrobe [15] on the anti–pernicious–anemia effect of yeast resulted from his observation that diets "supposedly" lacking in the "extrinsic" factor failed to produce macrocytic anemia in animals. In searching for the cause of failure of these experiments, he found in testing each constituent of the diet fed to the animals that brewers' yeast when given to a patient with pernicious anemia caused a well marked hemopoietic effect. Studies were then begun to determine: (1) whether oral administration of yeast regularly causes a hemopoietic effect in patients with pernicious anemia; (2) whether the potency of yeast can be enhanced by preliminary mixing with gastric juice; (3) whether the antianemic effect of yeast is dependent on the persistence

15. Wintrobe, M. M.: Antianemic Effect of Yeast, Am. J. M. Sc. **197**:286, 1939.

of the intrinsic factor in the patient, and (4) the nature of the active substance in yeast and its relation to the antianemia principle contained in liver.

An excellent review of the literature dealing with the effectiveness of yeast in the treatment of pernicious anemia is given. From this it is concluded that autolyzed yeast in amounts of 45 Gm. or more daily was effective in about one third of the cases of pernicious anemia in which it was tested. Smaller doses were effective after incubation with gastric juice. It appears to have been assumed without adequate study that nonautolyzed yeast does not possess antianemia potency.

After studying the effect of nonautolyzed yeast on patients in relapse (in doses of 1 to 2 Gm. per kilogram of body weight daily and a maintenance dose of 0.3 to 0.8 Gm. per kilogram daily), it was concluded that dehydrated brewers' yeast given orally "may" cause a hemopoietic response in cases of pernicious anemia which is as great as that produced by oral administration of liver extract derived from a quantity of liver two to eight times the weight of the brewers' yeast used. In the opinion of the author, the effectiveness of yeast may be due to its high concentration of extrinsic factor. This may react with even a minute amount of intrinsic factor, which is known to be present in the gastric secretions of some patients with pernicious anemia. Another equally plausible explanation, however, is that the antianemia factor in yeast differs from that in beef muscle not only quantitatively but qualitatively. According to Wintrobe, this statement is supported by his observations that yeast resembles in its antianemia effect the factor or factors in liver and desiccated hog stomach when given orally. It is his opinion, furthermore, that since knowledge of the physiologic disturbance associated with pernicious anemia and of the chemical nature and mode of action of the "extrinsic," "intrinsic" and "antianemic" principles is imperfect, one is not justified in drawing conclusions concerning the nature of the antianemia material in yeast. There is no positive evidence that the yeast factor is one of the B vitamins. For this purpose, studies have also been made of sources of these vitamins other than yeast, which include observations on the hemopoietic effect of wheat embryo, egg white, rice polishings, riboflavin and nicotinic acid. It has not been demonstrated that there is a relation between any one of the B vitamins and the antianemia substance.

Wintrobe, Samter and Lisco [16] have attempted to produce in young pigs a condition similar to pernicious anemia in man by giving a diet adequate in all respects except in some factor supplied by brewers' yeast.

16. Wintrobe, M. M.; Samter, M., and Lisco, H.: Morphologic Changes in Blood of Pigs, Associated with Deficiency of Water-Soluble Vitamins and Other Substances Contained in Yeast, Bull. Johns Hopkins Hosp. **64**:399, 1939.

Although anemia of variable severity and degree of macrocytosis appeared in the animals, the results were equivocal so far as production of the characteristic blood picture of pernicious anemia was concerned. The present studies confirm those made in 1938, in which a dietary deficiency was followed apparently by changes in the posterior columns of the spinal cord, the peripheral nerves and the "dorsal root ganglion cells."[17] Although their observations do not disprove that thiamine, riboflavin and nicotinic acid have an effect on blood formation, the authors conclude that the anemia which they observed appeared to be due to some other component of yeast. In 4 animals with anemia produced by the method just described, yeast therapy was followed by reticulocytosis and partial or complete relief of the anemia. A purified liver extract had no effect, and a cruder extract was used, likewise without result; but it is possible that an infection in the animal inhibited the response.

Heinle and Miller,[18] after studying the response of patients with pernicious anemia to yeast, do not agree with Wintrobe and his associates[17] that this material contains some hemopoietic factor specific for the disease. In 2 patients with pernicious anemia a reticulocyte response was obtained after the administration of dried brewers' yeast. This response was neither as great as that evoked with a minimal amount of ventriculin calculated to produce maximal reticulocytosis nor as great as that resulting from daily intramuscular injections of unconcentrated liver extract. It was considered by these observers that the response to yeast resulted from administration of an excess of extrinsic factor in the presence of greatly diminished but not completely absent intrinsic factor. It is their conclusion that the assumption that yeast contains a hemopoietic substance which is specific for pernicious anemia is unnecessary.

Foy and Kondi,[19] in studying nutritional macrocytic anemia as seen in Macedonia, observed that it responds equally well to a highly concentrated liver extract and to less purified preparations. This work suggests that the conclusion of Wills and Evans (1938) and Napier (1939) that tropical macrocytic anemia as seen in India is not benefited by highly purified liver extracts does not apply to the type of nutritional anemia

17. Wintrobe, M. M.; Mitchell, D. M., and Kolb, L. C.: Sensory Neuron Degeneration in Vitamin Deficiency: Degeneration of Posterior Columns of Spinal Cord, Peripheral Nerves, and Dorsal Root Ganglion Cells in Young Pigs Fed Diet Containing Thiamin (B_1) and Riboflavin But Otherwise Deficient in Vitamin B Complex, J. Exper. Med. **68**:207, 1938.

18. Heinle, R. W., and Miller, F. R.: Yeast as Extrinsic Factor in Relation to Pernicious Anemia, J. Clin. Investigation **18**:257, 1939.

19. Foy, H., and Kondi, A.: Response of Nutritional Macrocytic Anaemia to Anahaemin, Lancet **2**:360, 1939.

treated by Foy and Kondi. Furthermore, the condition in India differs in other respects, as a high indirect van den Bergh reaction is rare, and glossitis is common.

An investigation was made by Wigodsky, Richter and Ivy [20] to determine whether the fetal liver contains the anti-pernicious-anemia factor. According to them, it is likely that the fetus is entirely lacking in the extrinsic factor except for that present in the amniotic fluid and in the small amount of detritus which collects in the gastrointestinal tract. It is improbable, however, that either of these serves as a source of the extrinsic factor. Although these two statements may be correct, proof is not presented by the authors. Such an assumption seems somewhat risky to us, as the exact nature of the extrinsic factor is unknown at present. The prompt reticulocyte responses together with the return to normal blood pictures in 3 cases gave indisputable proof of the presence of the anti-pernicious-anemia principle in fetal bovine livers. Since it is assumed that the fetus is completely lacking in the extrinsic factor, it is suggested that the anti-pernicious-anemia principle is conveyed to the fetal liver by passing from the circulation of the mother through the placenta into the fetal circulation. This conclusion is in accord with the view that withdrawal of the anti-pernicious-anemia principle by the fetus may be one cause of the macrocytic anemia of pregnancy. It is interesting to note that there is a variance between the results observed by these authors after administering bovine liver and those obtained by Wintrobe, Kinsey, Blount and Trager,[21] who concluded that extracts of fetal swine liver were without effect when administered to patients with pernicious anemia. The authors are unable to account for this difference in results but suggest that (1) there may be a difference in permeability of the placenta of the pig and that of the cow or (2) the liver factor which is effective in the treatment of pernicious anemia is not required by the fetus for the maturation of red blood cells. This suggestion receives some support from the observation of Ivy and others that the injection of potent liver extract into pregnant rats and rabbits failed to reduce the size of the red blood cells of the newborn. It should be noted, however, that Stasney, Higgins and Mann [22] have demonstrated that a concentrate of normal human or

20. Wigodsky, H. S.; Richter, O., and Ivy, A. C.: Presence of Anti-Pernicious Anemia Factor in Extract of Fetal Bovine Livers, Am. J. M. Sc. **197**:750, 1939.

21. Wintrobe, M. M.; Kinsey, R. E.; Blount, R. E., and Trager, W.: Studies of Blood Formation in the Fetus and Newborn: III. Relation of Anti-Anemic Principle; Assay of Fetal Liver and Placental Extracts in Cases of Pernicious Anemia and in Mosquito Larvae, Am. J. M. Sc. **193**:449, 1937.

22. Stasney, J.; Higgins, G. M., and Mann, F. C.: Effect on Developing Red Blood Cells in Fetus of Administering Human and Hog Gastric Juice to Adult Rat During Pregnancy, Am. J. M. Sc. **197**:690, 1939.

swine gastric juice injected intraperitoneally into pregnant rats reduced the diameters of the red blood cells in newborn pups.

Stasney, Higgins and Mann [22] have employed the novel method of observing the effect of anti-pernicious-anemia substances in the physiologic macrocytosis of fetal white rats as a test for the principles governing hemopoiesis. This is based on the suggestion of Wintrobe and Schumacher that the macrocytosis observed in patients with pernicious anemia and that observed in fetal blood may both result from an inadequate amount of the essential antianemia principle. The technic used in the present investigation was to study the effect on the erythrocytes in young rats at birth of injecting concentrated normal gastric juice of man and swine into pregnant rats. The authors discovered that both human and swine gastric juices contain a substance which when injected into the pregnant adult rat accelerates the reduction in size and volume of the developing red blood cells of the newborn rat. Furthermore, it is concluded that these changes in the erythrocytes are proportional to the amount of gastric juice given to the adult rat during pregnancy and that the active substance is thermolabile. As a result of these experiments the authors suggest that the physiologic macrocytosis which occurs normally in the mammalian fetus may be due to an inadequate amount of the antianemia principle provided by the mother. The possibility that this effect on the fetal red blood cells may be utilized as a method of assaying the potency of the antianemia principle is considered. It is stated that the reaction is definite and that the extent of the decrease in size of the cells bears a direct relation to the amount of the principle administered. Additional study, however, is desirable in order to evaluate their method of bioassay.

In cases of untreated pernicious anemia, Schindler and Serby [23] by means of the gastroscope observed superficial gastritis, superficial gastritis plus atrophic gastritis and patchy or diffuse atrophy. After treatment the pathologic process persisted, disappeared or progressed. These authors confirm the previous observations of others that mucosal polyps are frequently present in the stomachs of patients with pernicious anemia.

A case of pernicious anemia unassociated with achlorhydria is reported by Finney.[24] From the description it seems likely that hepatic disease was present.

Statistical data on the incidence of symptoms in 580 patients with pernicious anemia are given by Isaacs.[25] Of these, ease of fatigue was

23. Schindler, R., and Serby, A. M.: Gastroscopic Observations in Pernicious Anemia, Arch. Int. Med. **63**:334 (Feb.) 1939.

24. Finney, J. O.: Pernicious Anemia Unassociated with Achlorhydria, Ann. Int. Med. **12**:1521, 1939.

25. Isaacs, R.: Diagnosis and Treatment of Pernicious Anemia, J. Indiana M. A. **32**:607, 1939.

outstanding in 85.1 per cent; numbness, in 81.2 per cent; tingling of the fingers and toes, in 74.3 per cent; shortness of breath, in 64.3 per cent; symptoms referable to the stomach, in 62.6 per cent; constipation, in 54.3 per cent; palpitation, in 49.3 per cent; edema, in 43.9 per cent; loss of appetite, in 43.9 per cent; difficulty in walking, in 43.6 per cent; symptoms referable to the bladder, in 35.0 per cent; dizziness, in 27.9 per cent; poor memory, in 26.8 per cent; diarrhea, in 26.5 per cent; pain, in 20.3 per cent, and stiffness, in 12.2 per cent. In most of the patients the disease developed between the ages of 35 and 65 years, with the peak of the distribution curve at 55 years. It appeared with equal frequency in the two sexes. The average length of the ear for the men was 7 cm. and for the women 6.5 cm., as compared with 6.7 and 6.1 cm. respectively for the general population. For treatment, 2 to 5 units of an antianemia medicament per day is recommended for very sick persons, with a maintenance dose of usually not less than 1 unit a day. Basophilia of the granules of the neutrophils, indicating pyogenic infection, calls for an increase to 3 to 5 units a day. Moore, Arrowsmith, Welch and Minnich [26] found that with patients with addisonian pernicious anemia in relapse there was no demonstrable increase in the elevated values for serum iron when ferrous salts were given orally. However, after a remission induced by administration of liver normal absorption curves were noted, suggesting the possibility of selective absorption or rejection of iron by the mucosa of the intestine, depending on the state of the tissues.

Jacobson [27] suggests that the argentaffin cells of the stomach are possibly the ones which secrete the antianemia enzyme. They are located in the places where the enzyme is secreted, and they are absent or greatly reduced in number in cases of pernicious anemia and sprue. Their number was not observed by Jacobson to be diminished in cases of "secondary anemia" or of macrocytic anemia not responding to liver extract.

Berlin [28] found that during a relapse the blood of a patient with pernicious anemia contains less hemolytically active lysocithin than does normal serum. This probably results from the reduced function or lack of lecithinase, which the lysocithin forms from the serum lecithin. During remission the level of blood lysocithin returns to normal.

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26. Moore, C. V.; Arrowsmith, W. R.; Welch, J., and Minnich, V.: Studies in Iron Transportation and Metabolism: IV. Observations on the Absorption of Iron from the Gastro-Intestinal Tract, J. Clin. Investigation **18**:533, 1939.

27. Jacobson, W.: The Argentaffine Cells and Pernicious Anaemia, J. Path. & Bact. **49**:1, 1939.

28. Berlin, R.: Ueber die Herabsetzung des Hämolysingehalts und das Fehlen der spontanen Hämolysinbildung im Serum bei Anaemia perniciosa, Acta med. Scandinav. **98**:425, 1939.

Bruner [29] found that the leukocytosis following injection of liver extract is not specific for the anti-pernicious-anemia factor. The leukocytosis is not due to active granulopoiesis but to a redistribution in the capillary bed.

Schultz [30] found high concentrations of glutathione in the erythrocytes of patients with pernicious anemia or with myelogenous leukemia. With the former condition there was a drop in both the total concentration of glutathione and the oxidized fraction after treatment, which induced considerable clinical improvement without causing the red blood cell volume to reach normal.

While sodium nucleinate and pentose nucleotide induce peripheral leukocytosis with hastened maturation of granulocytes in the marrow, Nordenson [31] found that this reaction does not take place in cases of infection or of pernicious anemia.

Veer [32] feels that the red precursor of melanin may be of importance as an antianemia principle in cases of pernicious anemia and that premelanin may play a part in hemopoiesis.

Sturgis,[33] in an analysis of the cause of death of 147 patients with pernicious anemia (90 men and 57 women), found that only 32 per cent died of lesions directly associated with pernicious anemia; these were mostly complications referable to the spinal cord. Involvement of the central nervous system and complications referable to the bladder indicated an unfavorable prognosis. Of the deaths not due to pernicious anemia, heart disease, cancer, apoplexy, pneumonia, trauma and nephritis were prominent causes. At the end of three years, 63 per cent of the treated patients were alive (as compared with 24 per cent in Cabot's 1915 summary), and 35 per cent were still living at the end of five years (Cabot's series, 11 per cent).

High values for blood magnesium characterize pernicious anemia in relapse, but Bang and Ørskov [34] found that normal values were present during remission. On the basis of the magnesium studies the authors conclude that in pernicious anemia there is a short life of the

29. Bruner, H. D.: Leukocytosis Following Parenteral Administration of Liver Extract in Man, Am. J. Physiol. **127**:58, 1939.

30. Schultz, M. P.: The Concentration of Glutathione in the Erythrocytes of Patients with Rheumatic Fever, Pub. Health Rep. **54**:264, 1939.

31. Nordenson, N. G.: Experimental Leucocytosis in Man, Quart. J. Med. **8**:311, 1939.

32. Veer, W. L. C.: Mélanin et ses precurseurs, Rec. d. trav. chim. d. Pays-Bas **58**:949, 1939.

33. Sturgis, C. C.: An Analysis of the Causes of Death in One Hundred and Fifty Fatal Cases of Pernicious Anemia Observed Since 1927, Tr. A. Am. Physicians **54**:46, 1939.

34. Bang, O., and Ørskov, S. L.: The Magnesium Content of the Erythrocytes in Pernicious and Some Other Anemias, J. Clin. Investigation **18**:497, 1939.

red blood cells with an increased rate of destruction. Remission is the result of stabilization of the red blood cells.

Pennetti [35] found that while the oxalic acid content of the blood in cases of hypochromic anemia and of the anemia of hemorrhage is within normal limits, in cases of pernicious anemia, of hepatic insufficiency and of phenylhydrazine anemia it is increased.

In patients with anemia, Ellis and Faulkner [36] found common circulatory characteristics to be cardiac enlargement, systolic murmurs, lowering of the systolic and diastolic pressures and abnormal electrocardiographic records (depression of the S-T segment and flattening or inversion of the T waves in lead I or in leads I and II). After treatment, as in cases of pernicious anemia, many of these abnormalities disappear or become less marked.

Cotti [37] reports that in cases of hemolytic icterus and pernicious anemia there is an increase in the excretion of porphyrin which appears to be independent of the amount of hemolysis.

In order to develop a formula which would represent reticulocyte production in terms of the time necessary to complete the reticulocyte response, Friedman, Isaacs and Lufkin [38] found the "average daily reticulocyte per cent." This figure which increases with the decrease in the erythrocyte count on the day that treatment was started (Eo), is expressed by the formula $\frac{20.2 - 4.1\ Eo}{1 + 0.25\ Eo}$. It takes into account the varying periods required in different cases to complete the "reticulocyte response."

Paddock and Smith [39] found that the thrombopenia associated with pernicious anemia in relapse is not a differentiating feature from other macrocytic anemias. After therapy the increase of platelets is parallel to that of erythrocytes.

Patrassi and Crepet [40] describe a patient with splenomegaly and hyperchromic anemia of the pernicious anemia type in whose case hepato-

35. Pennetti, G.: Metabolismo dell' acido ossalico ed emopatie, Haematologica **20**:153, 1939.

36. Ellis, L. B., and Faulkner, J. M.: The Heart in Anemia, New England J. Med. **220**:943, 1939.

37. Cotti, L.: Ricombio emoglobinico e ricambio porfirinico in condizioni anemiche con particolare riguardo all'anemia perniciosa: Nota preliminare, Boll. Soc. ital. biol. sper. **14**:710, 1939.

38. Friedman, A.; Isaacs, R., and Lufkin, A.: "The Average Daily Reticulocyte Response" During Therapy in Pernicious Anemia, J. Lab. & Clin. Med. **24**: 677, 1939.

39. Paddock, F. K., and Smith, K. E.: The Platelets in Pernicious Anemia, with a Review of the Literature, Am. J. M. Sc. **198**:372, 1939.

40. Patrassi, G., and Crepet, M.: Sulle reticolo-endoteliosi ad orientamento megaloblastico (splenomegalia pernicioso-emolitica e leucemia monocitica a screzio eritremico), Haematologica **20**:301, 1939.

therapy gave mediocre results, while splenectomy was followed by improvement. Similar cases in the literature are classed according to the prevalence of one of the component factors, such as hemolytic icterus. Even after disappearance of the collateral symptoms (achylia, glossitis) the disease continues to resemble pernicious anemia. Histologic studies of the spleen as well as of an enlarged axillary lymph node in the authors' case revealed hyperplastic reticuloendotheliosis localized predominantly or exclusively in the spleen, on which depended the myeloblastic transformation and the hyperhemolytic syndrome. These conclusions agree with the interpretation of pernicious anemia as a form of hemohistiocytosis (Ferrata). Patrassi and Crepet consider that megaloblastosis may be considered a sign of activation of the reticuloendothelial system and may be compared with the various systemic hematopathies, with more or less marked participation of the reticuloendothelial system.

Middleton and Wakerlin,[41] in studying the effect of liver extract on Paramecium, found that it did not change the rate of fission significantly. In high concentration and with inactivated liver extract the rate of fission was delayed.

Tschesche and Wolf [42] prepared an active liver extract, of which 40 mg. was a sufficient maintenance dose for a patient for four weeks after injection. There was little or no biuret reaction, and a ninhydrin reaction occurred before and after hydrolysis. The material was a white powder giving a slightly colored solution. The composition was: carbon, 50 per cent; hydrogen, 7 per cent; nitrogen, 14.5 per cent, and sulfur, 0.6 per cent. The substance is precipitated by Reinecke's acid, by rhodanilic acid and by one-half to two-thirds saturation with ammonium sulfate. It does not dialyze through heavy parchment. The Molisch, Millon, acriflavine, purine, pterine, reduced sugar and phosphoric ester reactions are negative.

Murphy and Howard [43] report the almost unique experience of being able to maintain 133 patients with pernicious anemia at an erythrocyte level of 5,000,000 per cubic millimeter by intramuscular injection of a liver extract at average intervals of three and seven-tenths weeks and at intervals of three and six-tenths weeks with a more concentrated extract. They found that neither sex nor age definitely influences the

41. Middleton, A. R., and Wakerlin, G. E.: Effect of Patenteral Liver Extract on the Fission Rate of Paramecium Caudatum, Proc. Soc. Exper. Biol. & Med. **42**:442, 1939.

42. Tschesche, R., and Wolf, H. J.: Ueber den Wirkstoff der Leber gegen perniziöse Anämie, Naturwissenschaften **27**:176, 1939.

43. Murphy, W. P., and Howard, I.: Use of Concentrated Liver Extracts in Pernicious Anemia: Survey of Maintenance Treatment of One Hundred and Seventy-Six Patients Under Continuous Observation for from Six Months to Six and One-Half Years, J. A. M. A. **112**:106 (Jan. 14) 1939.

amount of anti-pernicious-anemia substance necessary for maintenance, although 27 patients above 70 years of age required injections at intervals of two and four-tenths weeks to maintain an average red blood cell count of 4,590,000 per cubic millimeter, as compared with 5 patients younger than 39 years who required injection at intervals of four and one-tenth weeks to maintain a red blood cell count of 5,250,000. "Treatment," they conclude, "should be individualized according to each patient's needs, determined on the basis of the patient's clinical condition and erythrocyte counts made at desirable intervals."

In the early treatment of pernicious anemia, Jahsman [3] gives 195 U. S. P. units parenterally the first week, 45 units the second week and 15 units each week thereafter until the red blood cell count reaches 4,500,000 per cubic millimeter, which usually requires six to eight weeks. The maintenance dose recommended by Jahsman is 15 units twice a month. Larger doses are required when infection is present. Adequate liver therapy will prevent the development or progress of changes in the spinal cord, but when changes in the central nervous system are marked, large doses of liver extract are needed. Jahsman feels that iron, dilute hydrochloric acid, vitamin medication, physical therapy and blood transfusions have a definite place in certain cases and at the proper time. Vitamin B_1 or vitamin B_2 proved to be valuable in treating the neural lesions associated with pernicious anemia when given parenterally in doses of 2 mg. for thirty injections and of 10 mg. for twenty-four injections in a three month period by Mussio-Fournier and Rawak.[44] The treatment was effective even after five or six years of the disease, and amelioration of the nervous symptoms appeared even before the blood had returned to normal.

In subjects with pernicious anemia the bone marrow of the femur was found by Keilhack [45] to have normal amounts of "protein" but an excess of "albumin."

Jones [46] describes the reactions of 2 Negro patients to injections of liver extract. The first showed urticaria after the injections; the second, a reaction involving the vascular, gastrointestinal and respiratory apparatus. Cutaneous reactions and reagins to the liver extract were demonstrated. Such sensitivity disappears after a time, and desensitization is possible. For this type of patient it may be necessary to change the therapy or the route of administration (oral).

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44. Mussio-Fournier, J. C., and Rawak, F.: Action thérapeutique de la vitamine B, dans la myélose funiculaire de l'anémie pernicieuse, Rev. neurol. **70**: 604, 1938.

45. Keilhack, H.: Ueber das Eiweiss im normalen und pathologisch veränderten Knochenmark des Menschen, Deutsches Arch. f. klin. Med. **182**:57, 1938.

46. Jones, C. A.: Allergic Reactions Following Parenteral Administration of Liver Extract, Internat. Clin. **3**:258, 1939.

Wilkinson [47] describes a case of pernicious anemia in a man 26 years of age with neurologic involvement. There was a rapid response to liver extract and vitamin B_1. The patient's mother also had pernicious anemia, but there were no neurologic symptoms.

Central Nervous System.—Neuropathic symptoms and signs occur in more than 80 per cent of patients with pernicious anemia. Worster-Drought and Shafar [48] point out that the peripheral neuritis may be associated with other types of anemia and is probably due to a vitamin deficiency. Van Baalen and Vroon [49] cite several cases of pernicious anemia to demonstrate the various psychic changes which may occur. They observed marked mental improvement with elimination of the anemia. It should not be forgotten, however, that psychosis in a case of pernicious anemia may also be due to toxic effects from dysfunction of the genitourinary tract, cerebral arteriosclerosis and cerebral pathologic changes similar to those observed in the posterior and lateral columns of the cord.

Twenty patients with a paralytic form of involvement of the central nervous system were observed by Rosenthal and Abel.[50] In the majority of instances prolonged and adequate antianemia therapy was effective in arresting, retarding, improving or preventing aggravation of the neuropathic symptoms. These investigators state that after adequate treatment with liver or potent liver extract they did not observe any recurrences or progression of symptoms.

In an effort to determine the cause of the degenerative changes in the cord associated with pernicious anemia, Wintrobe and his colleagues [51] performed several experiments on young pigs. These animals were put on a balanced diet with large amounts of yeast. The yeast was gradually reduced and replaced by thiamine, riboflavin and nicotinic acid. These substances were given alone or in various combinations. All the animals which received reduced amounts of yeast had ataxia. Definite pathologic change was noted in the posterior columns and in the sensory nerves. Whether the results of these experiments can be

47. Wilkinson, J. N.: Pernicious Anemia with Cord Involvement in a Young Adult: Case Report, Clin. Virginia Mason Hosp. **18**:19, 1939.

48. Worster-Drought, C., and Shafar, J.: Achlorhydric Hypochromic Anemia Associated with Peripheral Neuritis, Brit. M. J. **2**:273, 1939.

49. Van Baalen, J., and Vroon, M. P.: Mental Disorders in Pernicious Anemia, Nederl. tijdschr. v. geneesk. **83**:270, 1939.

50. Rosenthal, N., and Abel, H. A.: Observations on the Effects of Liver Extract in Pernicious Anemia, with Special Reference to the Paraplegic Form of Subacute Combined Sclerosis, J. Mt. Sinai Hosp. **5**:349, 1938.

51. Wintrobe, M. M.; Samter, M., and Lisco, H.: Changes in the Blood and Nervous System of Pigs Associated with Deficiency of Substances Contained in Yeast, J. Clin. Investigation **18**:494, 1939.

utilized to explain the changes in the spinal cord associated with pernicious anemia is debatable, as many patients with pernicious anemia have involvement of the lateral as well as of the posterior column.

GASTRIC JUICE AND THE ANEMIAS

The role of gastric juice in erythropoiesis and the importance of this function have been recognized for several years. Leroux and Vermes [52] discuss in detail the various types of anemia associated with interference with normal gastric secretion. In their opinion there are multiple exogenous and endogenous factors, and the anemia is dependent on the effectiveness and combination of the factors which predominate. Dhayagude and Khadlihar [53] studied the relation of true achlorhydria and anemia. In 39 patients with anemia there was absence of "free hydrochloric acid" in the gastric contents after stimulation with histamine. The authors compared the results of a single fractional test meal and histamine stimulation. They concluded that the latter test gives more reliable information and that little, if any, risk is attached to it. In their series of cases achlorhydria was usually associated with pernicious anemia, Witt's anemia, ankylostomiasis and pellagra.

In an effort to determine the nature of the hemopoietic activity of gastric juice, Heinle and Miller [54] prepared gastric juice for parenteral therapy. When the extracts were given intravenously to 2 patients with pernicious anemia in relapse, no response was observed in either. The authors concluded that the gastric juice alone was ineffective because there was no extrinsic factor in the parenteral tissues to provide a substrate for interaction.

Brunschwig and his co-workers [6] demonstrated the presence of a secretory depressant in the gastric contents of patients with pernicious anemia (see section on pernicious anemia).

The effect of normal and abnormal human gastric juice administered to the mother on the blood of newborn rats has been investigated by Schlicke.[55] He noted an acceleration of hemopoiesis in the fetus, indicated by an increase in the number of red blood cells in the circulating blood, and a decrease in the volume and diameter of the fetal red blood cells at birth. The erythropoietic substance, which he observed to be

52. Leroux, R., and Vermes, E.: Anémies "agastriques," Sang **13**:241, 1939.

53. Dhayagude, R. G., and Khadlihar, V. N.: True Achlorhydria and Anaemia, Indian J. M. Research **26**:705, 1939.

54. Heinle, R. W., and Miller, F. R.: Negative Effect of Gastric Juice Administered Intravenously to Patients with Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **40**:681, 1939.

55. Schlicke, C. P.: The Effect of Normal and Abnormal Human Gastric Juice, Administered to the Mother, on the Blood of Newborn Rats: Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:145, 1939.

present in variable amounts in normal human gastric secretions, was absent in the gastric contents of patients with pernicious anemia. He states that this substance is similar to the intrinsic factor of Castle, inasmuch as it can be inactivated by heating. Stasney, Higgins and Mann [22] report somewhat similar experiments. In addition to human gastric juice, they employed pig gastric juice. In the opinion of these authors the resulting erythropoietic changes are proportional to the amount of gastric juice injected into the mother. Since the results are so constant, it has been suggested that this method may be satisfactory for assaying the potency of antianemia material.

Von Bonsdorff [56] exposed liver extract in vitro to the effects of fresh tapeworm, Taenia saginata, Ascaris lumbricoides, boiled tapeworm and alcoholic extracts of the tapeworm and of the colon bacillus. The extract was then given to several patients with pernicious anemia in relapse. The expected reticulocyte response was obtained. The influence of the intestinal worms on the proteolytic activity in vitro of trypsin, papain, pepsin and human gastric juice was also investigated by von Bonsdorff.[56] His conclusions are most interesting. The aqueous extracts of the various worms had a definite inhibiting effect on the proteolytic activity of gastric juice on casein at a neutral p_H. The same extracts did not inhibit the action of trypsin, pepsin or gastric juice at a low p_H; on the contrary, hydrolysis, expressed as increased nitrogen in trichloroacetic filtrates, was more marked in digests containing worm emulsion. The worm proteins were quickly digested by trypsin, pepsin and papain but not by gastric juice at a p_H of 7.4. The addition of a broth culture of Bacillus coli did not noticeably affect the proteolytic activity of the enzymes or of the gastric juice at a neutral reaction. Tapeworms had considerable proteolytic effect on casein at a p_H of 7.4. This digestive process decreased quickly at a lower p_H and more slowly at a higher p_H. Within the range of neutrality and slight alkalinity there is autodigestion of the worm. The author suggests the possibility that the worm enzyme and cathepsin are identical.

MACROCYTIC ANEMIAS OTHER THAN PERNICIOUS ANEMIA

The pathologic physiology of the macrocytic anemias has been adequately reviewed by Rhoads,[57] Castle,[58] Benhamou,[59] Goodwin,[60]

56. von Bonsdorff, B.: Liver Extract Exposed to the Action of Intestinal Worms Does Not Lose Its Anti-Anemic Effect, Acta med. Scandinav. **100**:436, 1939; The Influence of Intestinal Worms on the Proteolytic Activity in Vitro of Trypsin, Papain and Especially of Human Gastric Juice at Neutral Reaction, ibid. **100**:459, 1939.

57. Rhoads, C. P.: Vitamins: Vitamin B_2 Therapy, Conferences on Therapy, J. A. M. A. **113**:297 (July 22) 1939.

(Footnotes continued on next page)

Davidson,[61] Blum[62] and Wintrobe.[63] It is a generally accepted fact that food (extrinsic factor) interacts with gastric juice (intrinsic factor) to produce the erythrocyte-maturing substance. This product is absorbed in the intestine, stored in the liver and released to the bone marrow as needed. Any interference in this chain of events results in macrocytic anemia.

Onhauser and Mitchell[64] describe a case of pernicious anemia of pregnancy. The hematologic diagnosis was based on the presence of a megaloblastic marrow. It is the opinion of these authors that, since the patient had an adequate diet, the anemia was the result of a deficiency of the intrinsic factor. This view is directly opposed to that of Goldhamer, Fritzell and MacKinnon,[65] who produced a remission in a patient with pernicious anemia of pregnancy by feeding a high protein diet (extrinsic factor). Ritter and Crocker[66] describe a third case of macrocytic anemia in pregnancy, with a similar type of anemia in the newborn infant. From the results of their experiments with fetal bovine livers, Wigodsky and his co-workers[20] suggest that pernicious anemia of pregnancy is probably due to removal of too much of the erythrocyte-maturing factor from the mother by the fetus.

Red blood cell fragility in 40 patients with tropical macrocytic anemia was studied by Evans and Wills.[67] The median corpuscular fragility represented the concentration of salt solution which produced 50 per cent hemolysis. An analysis of their results revealed that in "complicated cases" of tropical macrocytic anemia there is increased fragility of the red blood cells, a fact which often masks the decreased fragility present in cases in which no complications occur.

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58. Castle, W. B.: The Diagnosis and Treatment of Anemia, Tr. & Stud. Coll. Physicians, Philadelphia **7**:129, 1939.

59. Benhamou, E.: Le traitement des anémies macrocytiques non biermériennes, Presse méd. **47**:755, 1939.

60. Goodwin, R. Q.: Macrocytic Anemias, South. M. J. **32**:641, 1939.

61. Davidson, L. S. P.: The Mechanism of Megoblastic Blood Formation, Edinburgh M. J. **46**:474, 1939.

62. Blum, L. L.: Newer Concepts in the Interpretation of Anemias, J. Indiana M. A. **32**:120, 1939.

63. Wintrobe, M. M.: The Choice of Methods for the Correction of Anemia, Internat. Clin. **2**:44, 1939.

64. Onhauser, V. F., and Mitchell, R.: A Case of Pernicious Anemia of Pregnancy, Canad. M. A. J. **41**:67, 1939.

65. Goldhamer, S. M.; Fritzell, A. I., and MacKinnon, F.: The Role of the Protein Level Intake in the Production of Remissions in Macrocytic Anemias, J. Clin. Investigation **18**:481, 1939.

66. Ritter, J. A., and Crocker, W. J.: Macrocytic Anemia of Pregnancy and Anemia of the Newborn, Am. J. Obst. & Gynec. **38**:239, 1939.

67. Evans, B. F. D., and Wills, L.: Red Cell Fragility in Tropical Macrocytic Anaemia, J. Path. & Bact. **48**:437, 1939.

Eight monkeys were observed after gastrectomy by Bussabarger and his co-workers [68] for two to three years. None had macrocytic anemia. Bachrach and Fogelson,[69] using dogs, removed seven-eighths of the stomach, all of the duodenum and 30 cm. of the jejunum. Macrocytic anemia was never noted. The authors conclude that hemopoiesis in dogs may be different from that in man or that there may be some factor other than that in the stomach or the duodenum which is essential for erythropoiesis.

Ten patients with macrocytic anemia associated with various lesions of the bowel were observed by Sturgis and Goldhamer.[70] Brock [71] also reports the occurrence of megalocytic anemia in patients with intestinal strictures. He considers that a multiple deficiency was present as a result of faulty absorption. Nontropical sprue complicated by anemia is reported by Frostad [72] and Rodriquez-Molina.[73] In the series of cases analyzed by Rodriquez-Molina, macrocytic anemia was present in 90 per cent of the patients, normocytic anemia in 7 per cent, simple microcytic anemia in 1 per cent and hypochromic anemia in 2 per cent.

Macrocytic anemia due to disease of the liver from various causes is reported by Burgess and Maclaren,[74] by Townsend and Braunstein [75] and in a discussion of a Cabot case.[76] A most unusual series of experiments was performed by Sydenstricker and his colleagues [77] with liver extract prepared from a pellagrin. When this extract was administered parenterally to a patient with pernicious anemia a prompt response was obtained. Pellagrins treated with a similar extract failed to respond but

68. Bussabarger, R. A.; Ivy, A. C.; Wigodsky, H. S., and Gunn, F. D.: The Effect of Gastrectomy on the Monkey, Ann. Int. Med. **13**:1028, 1939.

69. Bachrach, W. H., and Fogelson, S. J.: The Role of the Upper Gastrointestinal Tract in the Etiology of Pernicious Anemia, J. Lab. & Clin. Med. **24**: 249, 1938.

70. Sturgis, C. C., and Goldhamer, S. M.: Macrocytic Anemia, Other Than Pernicious Anemia, Associated with Lesions of the Gastrointestinal Tract, Ann. Int. Med. **12**:1245, 1939.

71. Brock, J. F.: Intestinal Stricture and Megalocytic Anaemia, Lancet **1**:72, 1939.

72. Frostad, S.: A Case of Non-Tropic Sprue with Normo- and Megaloblasts in the Peripheral Blood, Acta med. Scandinav. **99**:257, 1939.

73. Rodriquez-Molina, R.: Hematology of Sprue: Report on One Hundred Cases in Puerto Rico, Puerto Rico J. Pub. Health & Trop. Med. **15**:89, 1939.

74. Burgess, N., and Maclaren, C.: A Case of Pigmented Eczema with Macrocytic Anaemia, Brit. J. Dermat. **51**:207, 1939.

75. Townsend, S. R., and Braunstein, A. L.: Hyperchromic Macrocytic Anemia in Association with Hodgkin's Disease, Canad. M. A. J. **41**:254, 1939.

76. Carcinoma of Pancreas with Metastases to Liver; Pernicious Anemia, Cabot Case 25232, New England J. Med. **220**:967, 1939.

77. Sydenstricker, V. P.; Schmidt, H. L., Jr.; Geeslin, L. E., and Weaver, J. W.: The Liver in Pellagra, Am. J. M. Sc. **197**:755, 1939.

subsequently showed improvement when commercial liver preparations were given intravenously. From their results the authors conclude that pernicious anemia and pellagra are due to different causes. They also suggest that normal livers contain a substance other than the erythrocyte-maturing factor which is absent in the livers of pellagrins.

Several years ago, Wilkinson and Israëls described a disease (achresthic anemia) characterized by macrocytic anemia due to inability of the bone marrow to utilize the erythrocyte-maturing factor, the presence of free hydrochloric acid in the gastric contents and a fatal prognosis. Wauchope and Leslie-Smith [78] and Mahler and Greenberg [79] describe cases which they consider typical of this syndrome.

HEMOLYTIC ANEMIA

The hemolytic anemias comprise a group of blood dyscrasias which have multiple etiologic factors. It is necessary to recognize the causative agent for purposes of diagnosis, prognosis and treatment. The hemolytic anemias of childhood are characterized by reticulocytosis, leukocytosis, hyperplastic bone marrow and occasionally bony adsorption. Parsons [80] lists erythroblastosis foetalis, acute hemolytic anemia, reactive reticulocytosis, congenital hemolytic jaundice, sickle cell anemia and Cooley's anemia as members of this group. The similarity of icterus gravis, congenital anemia of the newborn and erythroblastosis is pointed out by Miller [81] in a case study of a family in which all three diseases were present. Henderson [82] has studied several cases of anemia of the newborn and of early infancy. He states that the anemia of prematurity is an exaggeration of physiologic hemolysis, that it is hyperchromic and that the cause is unknown. In most instances the prognosis is good.

Congenital hemolytic jaundice, although it may manifest itself in infancy, can occur at any age. Mandelbaum [83] reports a case in which an initial crisis occurred in a patient 75 years old who was cured by splenectomy. The usual characteristics of the malady were present—

78. Wauchope, G. M., and Leslie-Smith, M.: Macrocytic Anaemia of the Achrestic Type, Lancet **2**:1518, 1938.

79. Mahler, A., and Greenberg, D.: A Case of Hyperchromic Macrocytic Anemia Refractory to Liver Extract, J. A. M. A. **112**:1150 (March 25) 1939.

80. Parsons, L. G.: The Haemolytic Anemias of Childhood, Lancet **2**:1395, 1938.

81. Miller, H. C.: The Familial Occurrence of Icterus Gravis, Congenital Anemia of the Newborn and Erythroblastosis Fetalis: Case Study, Yale J. Biol. & Med. **11**:363, 1939.

82. Henderson, J. L.: Anaemias of the Newborn and Early Infancy, Tr. Edinburgh Obst. Soc., 1938-1939, p. 63; in Edinburgh M. J., March 1939.

83. Mandelbaum, H.: Congenital Hemolytic Jaundice: Report of a Case of Congenital Hemolytic Jaundice; Initial Hemolytic Crisis Occurring at the Age of Seventy-Five; Splenectomy Followed by Recovery, Ann. Int. Med. **13**:872, 1939.

jaundice, an enlarged spleen, small round cells (which were fragile) and reticulocytosis. The unusual occurrence of ulcer of the leg in a case of hemolytic jaundice is noted by Taylor.[84] Such a lesion may be bilateral and usually occurs on the medial malleolus. Local therapy is of little value, but healing often results after splenectomy. Watson [85] reports a study of 35 patients with hemolytic jaundice. Twenty of these had microcytic anemia, increased fragility of the red blood cells and absence of autoagglutination. In the remaining 15, macrocytic anemia predominated; there was little, if any, evidence of increased fragility of the red blood cells, and autoagglutination occurred in 2 instances. The author calls attention to the fact that there was no parallelism between the anemia and the jaundice. This suggested sluggish excretion of bilirubin by the liver, which was considered beneficial rather than detrimental to the patient.

As an accurate method of determining the increased fragility of the red blood cells in cases of hemolytic jaundice, Guest and Wing [86] used the Van Allen hematocrit tubes. Measured amounts of red blood cells were drawn into standardized tubes and diluted with saline solution of varying concentrations. Changes in volume as well as beginning and complete hemolysis were noted.

One of the more serious complications often observed in association with the administration of sulfanilamide and sulfapyridine is hemolytic anemia. Koletsky [87] states that the anemia is not related to the type of infection, the dose of the drug or the concentration of the drug in the serum. He reported 2 deaths due to hemolytic anemia following treatment with sulfanilamide. Garvin [88] describes two types of hemolytic anemia: acute and chronic. The latter is mild, develops slowly and is not associated with jaundice, but there is excessive excretion of urobilinogen. The acute type has an abrupt onset in two to three days. Withdrawal of the drug and transfusions were beneficial to the patients. Antopol and his colleagues [89] note the occurrence of acute hemolytic

84. Taylor, E. S.: Chronic Ulcer of the Leg Associated with Congenital Hemolytic Jaundice, J. A. M. A. **112**:1574 (April 22) 1939.

85. Watson, C. J.: Hemolytic Jaundice and Macrocytic Hemolytic Anemia: Certain Observations in a Series of Thirty-Five Cases, Ann. Int. Med. **12**:782, 1939.

86. Guest, G. M., and Wing, M.: A Method for the Determination of Erythrocyte Fragility, Using Van Allen Hematocrit Tubes for the Measurement of Changes in Volume of the Cells in Hypotonic Salt Solutions, J. Lab. & Clin. Med. **24**:850, 1939.

87. Koletsky, S.: Fatal Hemolytic Anemia Following the Administration of Sulfanilamide, J. A. M. A. **113**:291 (July 22) 1939.

88. Garvin, C. F.: Complications Following the Administration of Sulfanilamide, J. A. M. A. **113**:288 (July 22) 1939.

89. Antopol, W.; Applebaum, I., and Goldman, L.: Two Cases of Acute Hemolytic Anemia with Auto-Agglutination Following Sulphanilamide Therapy, J. A. M. A. **113**:488 (Aug. 5) 1939.

anemia associated with autoagglutination following sulfanilamide therapy. Plummer and Ensworth [90] reported the presence of severe anemia in 270 patients with pneumonia treated with sulfapyridine. They also called attention to the fact that several of these patients had mild anemia. Similar results from the use of drugs of the sulfanilamide group are noted by Morgan and Detweiler,[91] Price and Myers [92] and MacLeod.[93] It is suggested by MacLeod that toxic effects from these drugs are more common than is expected and that more than routine studies should be employed to detect them.

Hemolytic anemia was produced in dogs and monkeys after administration of sulfanilamide by P'An.[94] Machella and Higgins [95] observed anemia in rats following the use of sulfanilamide. They conclude that the severity of the anemia varies with the dose of the drug and that recovery follows withdrawal of the drug. On the basis of the minimal concentration in the blood necessary to produce anemia, Richardson [96] compared the toxicity of sulfanilamide, sulfapyridine and diaminodiphenylsulfone. Sulfapyridine was the least toxic and diaminodiphenylsulfone the most toxic.

Erf and MacLeod [97] determined quantitatively the amount of urobilin excreted by 20 patients with pneumonia treated with sulfapyridine and employed this method as an index of hemolysis. The amount of urobilin excreted varied with the anemia, and both were directly proportional to the dose of the drug. All evidence of destruction of red blood cells disappeared when the sulfapyridine was withdrawn.

The effect of various hemolytic agents on red blood cells has been investigated by Dameshek, Schwartz and Singer.[98] They employed

90. Plummer, N., and Ensworth, H. J.: Sulfapyridine in the Treatment of Pneumonia, J. A. M. A. **113**:1847 (Nov. 18) 1939.

91. Morgan, J. R. E., and Detweiler, H. K.: The Hematologic Study of Seventy-Six Pneumonia Cases Treated with Sulfapyridine, Including a Fatal Case of Agranulocytosis, J. Lab. & Clin. Med. **25**:275, 1939.

92. Price, A. E., and Myers, G. B.: Treatment of Pneumococcic Pneumonia with Sulfanilamide, J. A. M. A. **112**:1021 (March 18) 1939.

93. MacLeod, C. A.: Chemotherapy of Pneumococcic Pneumonia, J. A. M. A. **113**:1405 (Oct. 7) 1939.

94. P'An, S. Y.: Observations on the Chronic Effect of Sulfanilamide in Dogs and Monkeys with Particular Reference to the Blood, Chinese M. J. **56**:111, 1939.

95. Machella, T. E., and Higgins, G. M.: Anemia Induced in Rats by the Administration of Sulfanilamide, Proc. Staff Meet., Mayo Clin. **14**:183, 1939; Anemia Induced in Rats by Means of Sulphanilamide, Am. J. M. Sc. **198**:804, 1939.

96. Richardson, A. P.: The Production of Anemia in White Mice by Sulfanilamide, Sulfapyridine and Diaminodiphenylsulfone, J. Pharmacol. & Exper. Therap. **67**:429, 1939.

97. Erf, L. A., and MacLeod, C. M.: Hemolysis from Sulfapyridine, J. Clin. Investigation **18**:472, 1939.

98. Dameshek, W.; Schwartz, S. O., and Singer, K.: Spherocytosis (and Increased Erythrocyte Fragility) as Indicators of Hemolytic Activity, with a Consideration of "Differential" Fragility, J. Clin. Investigation **18**:479, 1939.

this method in an attempt to distinguish the various types of hemolytic anemias. It was noted that distilled water, saponin, phenylhydrazine, lysolecithin and immune hemolytic serum would produce spherocytosis of varying degree, depending on the dose. The changes observed in the bone marrow and in the peripheral blood indicate that spherocytosis developed outside the bone marrow. It was also noted that all the spherocytes reacted in the same manner to varying dilutions of saline solution but differed in their reactions to the hemolysins. This physiologic difference is considered important in distinguishing the various hemolytic anemias.

Cases of Lederer's anemia with the characteristic blood picture are reported by Drummond,[99] Levy and Miller [100] and Boquien.[101] All of these investigators discuss the various possible etiologic factors and conclude that the cause is not known. They also state that transfusions are specific. McGavack [102] reports a similar case of acute hemolytic anemia in a 17 year old girl, but as transfusions did not aid the patient he feels that this was not a case of Lederer's anemia. Hamilton [103] describes a syndrome characterized by chills, fever, dark urine, oliguria and splenomegaly, occurring in a 2 year old boy. The patient had several remissions and relapses. The author expresses the opinion that this case simulated Lederer's anemia but believes that the condition is a distinct clinical entity and that it should be named "acute hemocytolytic anemia."

SICKLE CELL ANEMIA

Diggs and Bibb,[104] of Memphis, Tenn., present an excellent study of the status of the erythrocyte in 47 patients with active sickle cell anemia. They observed that in sealed cover slip preparations there occurs an increase in the carbon dioxide content of the serum in which the erythrocytes are suspended within a few hours. Coincidentally with this, the red blood cells assume many bizarre forms. The change is from the normal round shape with even distribution of hemoglobin to a many-pointed form, thick in one portion and thin in another. Elliptic, oat-shaped or crescent-shaped erythrocytes, which are present when the blood is drawn, have apparently passed through the process just

99. Drummond, J.: A Case of Lederer's Anaemia, South African M. J. **13**: 406, 1939.

100. Levy, W., and Miller, W. J.: Acute Hemolytic Anemia: Lederer Type, Am. J. Dis. Child. **58**:349 (Aug.) 1939.

101. Boquien, Y.: Trois cas -dont deux familiaux- d'anémie hémolytique aiguë (maladie de Lederer-Brill), Sang **13**:320, 1939.

102. McGavack, T. H.: Acute Hemolytic (Lederer's) Anemia, New England J. Med. **220**:140, 1939.

103. Hamilton, D. G.: A Case of Acute Haemocytolitic Anaemia with Haemoglobinuria, M. J. Australia **1**:305, 1939.

104. Diggs, L. W., and Bibb, J.: The Erythrocyte in Sickle Cell Anemia, J. A. M. A. **112**:695 (Feb. 25) 1939.

described and do not undergo further significant change. When the blood in sealed moist preparations is exposed to the air, the bizarrely shaped cells, which are in the initial stages of sickling, revert to the round forms, and the true sickle cells become less pointed but do not become round.

According to these observers, the typical characteristic sickle cell averages 10 to 20 microns in length and 2 to 4 microns in width. It is hyperchromic, elongated, pointed at each end and curved in the middle. Rarely is it observed in any other condition than true sickle cell anemia. The percentage of these abnormally shaped cells in stained films made in the usual manner varies from none to over 50 per cent; apparently there is no relation between the number of sickle cells and the severity of the anemia.

Measurements of the red blood cells of patients in whom less than 5 per cent of the cells were elongated showed marked anisocytosis and mean diameters which were greater than normal, averaging between 7.8 and 9.5 microns. The average mean corpuscular volume was 90 cubic microns; the average mean corpuscular hemoglobin was 29 micromicrograms, and the average mean corpuscular hemoglobin concentration was 32 per cent. These figures indicate that the erythrocytes in cases of sickle cell anemia are usually of the normocytic, normochromic type, with a tendency toward macrocytosis. The reticulocytes of the circulating blood are usually increased in the presence of active sickle cell anemia; in this series the average was 15 per cent.

The erythrocytes of patients with sickle cell anemia are more resistant than are normal cells to hypotonic saline solutions, and some of the cells even retain their hemoglobin in distilled water. In this study, hemolysis began in hypotonic salt solutions at an average of 0.34 per cent and was complete at 0.11 per cent, whereas the average figures for the control groups were 0.42 per cent and 0.32 per cent respectively. The resistance of erythrocytes of patients with the sickle cell trait in the absence of anemia was also slightly increased, as hemolysis began at 0.35 per cent and was complete at 0.2 per cent. Corresponding figures for the control group were 0.39 per cent and 0.27 per cent.

Mechanical shaking of oxalated or defibrinated blood at the rate of two hundred and fifty vibrations per minute did not cause a significant alteration in the red blood cell count or the cell volume in blood from normal persons or from patients with sickle cell anemia. When glass beads were added, however, and the carbon dioxide concentration in the air above the blood was increased, the red blood cells of patients with sickle cell anemia were destroyed more rapidly than were those of normal blood. It is concluded from these experiments that the carbon dioxide causes the red blood cells to become larger and the round cells in the blood of patients with sickle cell anemia to become sickled.

The sedimentation rate for patients with sickle cell anemia may be normal despite the presence of marked anemia. These observers interpret an increased sedimentation rate in the presence of this disease as indicative of some complication, such as active tuberculosis, salpingitis or badly infected ulcers of the leg.

Bunting [105] observed that sickled erythrocytes from patients with sickle cell anemia and the sickle cell trait did not form rouleaux and remained unsedimented after one hour of observation. Specimens of blood for this study were obtained from patients with sickle cell anemia and the sickle cell trait, and the percentage of sickle cells was increased to approximately 50 per cent by exposure to carbon dioxide. Specimens of the same blood which were not exposed to carbon dioxide and contained relatively few sickle cells formed rouleaux and sedimented at a rate of 23 to 70 mm. in one hour. These studies would suggest that the delay in settling of the red blood cells is proportional to the percentage of sickle cells present.

Arena [106] reports the case histories of 5 Negro children with sickle cell anemia, in whom the first manifestation of the disease was the appearance of signs and symptoms indicative of cerebral vascular disease. All had right hemiplegia. Reference is made to a relatively small number of similar cases in the literature. It is emphasized that thrombotic phenomena are important episodes in the life history of patients with this type of anemia and that obliterative vascular changes and thrombi are part of the pathologic picture. It is the belief of some that the tendency to capillary engorgement and arterial thrombosis may be due to the abnormal shape of the red blood cells, which prevents their ready passage through the capillaries, and the tendency of these cells to agglutinate. Infection with fever, which causes increased sickling, may be a factor in causation of the thrombosis. In 1 patient necropsy showed a tendency to occlusion of the large subarachnoid arteries, which is similar to the changes observed in the splenic vessels. The author concludes that splenectomy should be given a further trial for patients with splenomegaly who have constitutional symptoms and previously have had a vascular accident.

Josey [107] reports the case of a Negro boy aged 8 years with sickle cell anemia, who at the age of 4 years had attacks persisting for a week or more in which he had difficulty in speaking, swallowing and walking. Two years later left hemiplegia appeared, which persisted for six weeks.

105. Bunting, H.: Sedimentation Rates of Sickled and Non-Sickled Cells from Patients, Am. J. M. Sc. **198**:191, 1939.

106. Arena, J. M.: Sickle Cell Anemia, Cerebral Vascular Lesions Accompanying Anemia, J. Pediat. **14**:745, 1939.

107. Josey, A. I.: Sickle Cell Anemia with Cerebral Thrombosis (Case), South. M. J. **32**:915, 1939.

A year later, at the age of 7 years, the hemiplegia again occurred, and this time it was associated with aphasia. Fifteen weeks later the weakness on the left side was improved somewhat, and speech had partially returned. One year after this there was slight improvement in the patient's neurologic condition, but the general picture remained the same. This case is reported as probably representing recurrent cerebral thrombosis associated with sickle cell anemia.

Bridges [108] reviews the literature dealing with cerebral vascular accidents in patients with sickle cell anemia and states that in none of the cases thus far reported has a satisfactory account of the origin and nature of the cerebral clinical disturbances been offered. Two cases of sickle cell anemia with cerebral vascular manifestations are reported, with a discussion of the pathogenesis of the lesions of the central nervous system and a consideration of the general problem of the disease. It is suggested that the obliterative vascular changes in the spleen previously described by Diggs may occur likewise in the cerebral vessels from the same cause. From the studies reported by Bridges it is concluded that the clinical evidences of cerebral lesions may arise from two different pathologic changes. The large subarachnoid cerebral arteries may undergo gradual obliteration with final complete closure as a result of endarterial intimal proliferation and not of thrombosis. This process is identical with that which causes occlusion of the splenic arteries. A second obscure process also occurs, which is quite different from endarterial intimal proliferation. This change is in connection with the small intracerebral vessels and is responsible for multiple focal necroses and hemorrhages in the brain.

Page and Silton [109] report the effect of pregnancy in 2 cases of acute sickle cell anemia. One patient, aged 19, in whose case there were a red blood cell count of 1,660,000 per cubic millimeter and a hemoglobin concentration of 42 per cent, was first observed three weeks from term; liver extract, copper and iron were given orally. The patient had a normal spontaneous delivery, and seven months later the mother had no complaints referable to the anemia, although the red blood cell count was approximately 2,000,000 per cubic millimeter. The baby, whose blood did not show sickling, was in good condition at the age of 7 months. The second patient, aged 20 years, was five months pregnant when first seen; the red blood cell count was 1,920,000 per cubic millimeter and the concentration of hemoglobin was 35 per cent. She was acutely ill, and a clinical diagnosis of bilateral bronchopneumonia was made. Death occurred twenty-two hours after admission, and

108. Bridges, W. H.: Cerebral Vascular Disease Accompanying Anemia, Am. J. Path. **15**:353, 1939.

109. Page, E. W., and Silton, M. Z.: Pregnancy Complicated by Sickle-Cell Anemia, Am. J. Obst. & Gynec. **37**:53, 1939.

necropsy showed sickle cell anemia, thrombophlebitis of the pelvic veins, embolism of the pulmonary arteries with multiple infarcts, twin pregnancy (5 months) and severe siderofibrosis of the spleen. The authors conclude that pregnancy may be a factor in producing an exacerbation of the disease but that patients may be carried successfully to term when proper measures are employed.

ERYTHROBLASTIC AND LEUKOERYTHROBLASTIC ANEMIAS

Several examples of leukoerythroblastic anemia in adults have been described. Vaughan defined this condition as "an anemia characterized by the presence, in the peripheral blood, of immature red blood cells and a few immature white blood cells of the myeloid series." In 2 cases described by Vaughan and Harrison [110] there were splenomegaly, irregular density of the spongiosa of long bones and throughout the flat bones associated with decreased density of the cortex of the long bones, the inner edge of the cortex being frayed and irregular in appearance (myelosclerosis), leukoerythroblastic anemia and increased fragility of the red blood cells in hypotonic saline solutions, associated with increased thickness of the cells. The condition was confused at different stages of its evolution with polycythemia and leukemia. Cases have been described under the names erythroleukemia, atypical myeloid leukemia, aleukemic myelosis, myelophthisic splenomegaly, myelosclerosis, myelosis with osteosclerosis and myelosclerosis associated with a leukemoid blood picture.

Of the 3 cases described by Gear and Becker,[111] the condition in 2 was associated with carcinomatosis, and in 1, with multiple myelomatosis. The disease is grouped with Cooley's erythroblastic anemia, but the pathogenesis is essentially different.

Diamond [112] presents an excellent review of the general subject of erythroblastic anemias in infancy and childhood. In the first group is erythroblastemia secondary to some obvious underlying cause (excessive exposure to roentgen rays or to radioactive material, chemical and drug poisoning, generalized malignant disease with metastasis to the bone marrow, steatorrhea, recurrent and severe hemorrhage, chronic or severe infection, congenital syphilis, congenital malformations of the circulatory system or hemolytic anemia), while in the second group are anemias of unknown origin (Mediteranian anemia and the anemia of

110. Vaughan, J. M., and Harrison, C. V.: Leuco-Erythroblastic Anaemia and Myelosclerosis, J. Path. & Bact. **48**:339, 1939.

111. Gear, J., and Becker, L. H.: Leuco-Erythroblastic Anaemia: Report of Three Cases, South African M. J. **13**:13, 1939.

112. Diamond, L. K.: The Erythroblastic Anemias, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p. 57.

erythroblastosis foetalis). The treatment of Mediterranean anemia and of erythroblastosis foetalis is symptomatic and nonspecific, and the results are unsatisfactory.

Nittis [113] explains the peculiar structure of the diploe in cases of erythroblastic anemia by outward expansion of the marrow as a result of continuously stimulated hemopoiesis. The trabeculae connecting the two plates become elongated, producing a bristle-like appearance on the roentgen plate.

In a detailed description of 5 typical cases of Cooley's anemia, Francaviglia [114] notes that there was increased resistance of the red blood cells in the parent who transmitted the disease and in the apparently normal brothers and sisters of the patients. For patients with atypical forms of the disease with slow evolution, thyroid, liver extract and iron were of therapeutic value in prolonging life.

The essential pathologic features, as noted by Schiappoli [115] in 2 cases, are a process of general reabsorption of the bones with formation of new trabeculae, diffuse hyperplasia of the reticuloendothelial system, hemolytic anemia and increased medullary and extramedullary hemopoiesis. Constitution and familial predisposition are considered important factors in the disease, but the cause is unknown.

In cases of erythroblastic anemia with jaundice in children and adolescents, Acuña and Bonduel [116] found that damage to the liver was caused by the products of hemolysis. The peripheral blood in this condition is characterized by large numbers of immature red blood cells and leukocytes. The hepatomegaly and other features at times suggest von Jaksch's pseudoleukemia. The behavior of the pigments and their decomposition products is different from that observed with congenital splenomegalic hemolytic jaundice, suggesting that these are two different clinical forms of congenital hemolytic jaundice.

Andrus and Holman [117] removed the spleen from 4 children with Cooley's erythroblastic anemia. One died in five months, a second in two years. Two, alive three and one-half years and four years respectively after operation, were in fair condition, but the anemia persisted.

113. Nittis, S.: The Mechanism of the Production of Bone Changes in the Plastic Anemias, Univ. Hosp. Bull., Ann Arbor **5**:27, 1939.

114. Francaviglia, A.: Ricerche sul morbo di Cooley; studio clinico su alcuni casi di morbo di Cooley osservati in Puglia, Arch. per le sc. med. **68**:395, 1939.

115. Schiappoli, F.: Ricerche sul morbo di Cooley; il reperto anatomico, Arch. per le sc. med. **68**:457, 1939.

116. Acuña, M., and Bonduel, A. A.: Alteraciones hepáticas en el curso de las anemias erithroblásticas. Ictericias eritroblásticas, Prensa méd. argent. **25**:2444, 1938.

117. Andrus, W. DeW., and Holman, C. W.: Splenectomy in Various Blood Disorders, Ann. Surg. **109**:64, 1939.

In a case reported by Macklin, Lamont and Macklin,[118] erythroblastosis foetalis accompanied by hemolysis was present in a newborn girl. Of the other pregnancies of the mother, 5 of 7 ended in miscarriages or premature delivery, suggesting a possibility of a similar blood dyscrasia which prevented development of the fetus. The authors feel that the disease represents derangement of blood formation in the fetus rather than persistence of a normal fetal blood picture.

Thalheimer, Mezzetti and Gershon-Cohen[119] described a case of Cooley's Mediterranean anemia in a 14 year old Italian girl; this makes the seventh case of this type in the literature. The illness dated from the first year of life. Physical examination showed mongoloid facies, a large heart, a protruding abdomen, hepatomegaly and characteristic roentgen changes in bone. The spleen had been removed at the age of 5 years. The blood was characterized by hypochromic anemia and leukocytosis.

Moore and Pastore[120] noted erythroblastic splenomegaly in a pregnant Negress. Erythrogenic foci were found in the spleen, liver and lymph nodes, but the bone marrow was not grossly abnormal. It is thought that infection (pneumonia, tuberculosis, renal abscesses and rheumatic fever) combined with pregnancy induced the alterations in the hemopoietic tissue. There were some appearances in the internal organs resembling leukemia, and 10 per cent myeloblasts were observed in the peripheral blood.

Erythroblastic anemia in 2 brothers aged respectively 17 and 20 years is described by Atkinson.[121] There was no evidence of a hereditary origin of the disease, although the red blood cells of the father, the mother and one of 2 sisters showed greater resistance in diluted saline solution than did those of normal controls (hemolysis complete, 0.08 per cent; 0.04 per cent; 0.08 per cent; controls, 0.22 per cent to 0.28 per cent).

A case of acute erythromyelosis in a 25 year old woman is described by Chevallier and Ely.[122] Anemia, leukopenia, fever and a hemorrhagic tendency characterized the disease. On sternal puncture 82 per cent of the cells were observed to be erythroblasts, and in the peripheral blood nucleated red blood cells numbered 51,920 per cubic millimeter.

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118. Macklin, M. T.; Lamont, J. A., and Macklin, C. C.: Erythroblastosis Fetalis: Report of a Case, Am. J. Dis. Child. **57**:349 (Feb.) 1939.

119. Thalheimer, E. J.; Mezzetti, A., and Gershon-Cohen, J.: Cooley's Anemia (Mediterranean Anemia), with Report of a Case in an Adolescent, J. Pediat. **14**: 349, 1939.

120. Moore, R. A., and Pastore, J. B.: Note on Erythroblastic Splenomegaly Occurring During Pregnancy, Am. J. M. Sc. **198**:187, 1939.

121. Atkinson, D. W.: Erythroblastic Anemia: Report of Two Cases in Adult Siblings, with a Review of the Theories as to Its Transmission, Am. J. M. Sc. **198**:376, 1939.

122. Chevallier, P., and Ély, Z.: Erythromyélose aiguë, Sang **13**:106, 1939.

APLASTIC ANEMIA

Rhoads,[123] summarizing an extensive study of aplastic anemia, divides refractory anemia into five histologic types: that with hypocellular bone marrow, that with immature cellular marrow, that with active cellular marrow, that with sclerosis of the marrow and that with megakaryocytic marrow. The disease may have definite but temporary remissions, in some cases induced by splenectomy. In 6 cases definite exacerbations followed exposure to sunlight. Toxemia may play a part in the production of the disease, the several types having varying responses to cyclic chemical compounds of endogenous or exogenous origin.

Huber [124] studied the blood and bone marrow of relatives of 4 patients who died of panmyelophthisis. A common finding was neutropenia or lymphocytosis, suggesting a familial diathesis to disease of the bone marrow with congenital or inherited weakness of the marrow. The pathologic feature was imbalance of the neutrophil-leukocyte content of the blood.

Longsworth, Shedlovsky and MacInnes [125] found that the gamma globulin-albumin ratio in the serum of patients with aplastic anemia is above normal.

Rein and Wise [126] reported a case of aplastic anemia in a 30 year old woman after mapharsen treatment, with a fatal termination. There were multiple petechial and ecchymotic hemorrhages of the arachnoid, visceral pleura, epicardium, endocardium, renal capsules, ileum and cecum, with toxic hepatosis and hyperlastic splenitis.

A case of aplastic anemia following intravenous injection of a gold compound is reported by Wintrobe, Stowell and Roll.[127] Recovery followed nine blood transfusions and hysterectomy. These authors did not succeed in producing aplastic anemia by intravenous injection of a gold compound into rabbits. In cases collected from the literature, 6 patients with idiopathic aplastic anemia and 13 of a group with postarsenical aplastic anemia survived one year or longer.

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123. Rhoads, C. P.: Aplastic Anemia, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p. 31.

124. Huber, H.: Stammbaumuntersuchungen bei Panmyelophthisekranken, Klin. Wchnschr. **18**:1145, 1939.

125. Longsworth, L. G.; Shedlovsky, T., and MacInnes, D. A.: Electrophoretic Patterns of Normal and Pathological Human Blood Serum and Plasma, J. Exper. Med. **70**:399, 1939.

126. Rein, C. R., and Wise, F.: Mapharsen in Treatment of Syphilis in Office Practice: A Study Based on 2,342 Injections in One Hundred and Thirteen Patients, J. A. M. A. **113**:1946 (Nov. 25) 1939.

127. Wintrobe, M. M.; Stowell, A., and Roll, R. M.: Report of a Case of Aplastic Anemia Following Gold Injections in Which Recovery Occurred, Am. J. M. Sc. **197**:698, 1939.

In cases of aplastic anemia Jordan [128] finds that the lymphoid structure of the lymph nodes, the spleen and the marrow is identical. The predominant cell in the three tissues is the lymphocyte, which Jordan considers an immature polyvalent cell. The small lymphocytes grow to become large lymphocytes, which differentiate into erythrocytes in the venous sinuses and into granulocytes in the intervascular stroma.

Ingraham [129] reports a case of aplastic anemia with fatal termination, following the use of triarsen and bismuth salicylate during pregnancy. The red blood cell count before transfusion fell to 780,000 per cubic millimeter, and the terminal leukocyte count was 1,800 per cubic millimeter, with 5 per cent neutrophils.

In Boon's [130] case aplastic anemia followed arsphenamine therapy. Twenty-five transfusions totaling 12,540 cc. of blood were given, without evidence of spontaneous regeneration of blood. After the transfusions were discontinued there was a rise in the number of reticulocytes and of red blood cells, followed by recovery. The granulocytes recovered more slowly than did the red blood cells.

In the treatment of a moribund patient with aplastic anemia, Osgood, Riddle and Mathews [131] tried intravenous injection of bone marrow suspended in the donor's blood. The cells disappeared rapidly from the circulation. There was no untoward reaction, but the authors express doubt that there was any therapeutic benefit from the procedure. During fifty-two days, forty-three blood transfusions were given, totaling 21,870 cc. Death was due to sepsis with terminal bronchopneumonia. Pentose nucleotide and liver extract were ineffective.

HEMATOLOGIC CHANGES ASSOCIATED WITH INFECTION

Leukemoid reactions of the myeloid type have been classified recently by Heck and Hall.[132] These authors stress the fact that the hematologic picture simulates that of leukemia, but at autopsy there is no evidence to support this diagnosis. In the presence of pyogenic infections there are an increase in the polymorphonuclear neutrophils, increasing numbers of immature cells and degenerative changes of the leukocytes. The degree of alterations is dependent on the virulence of the organism, the

128. Jordan, H. E.: Aplastic Anemia, with Special Reference to the Significance of the Small Lymphocytes, Arch. Path. **27**:1 (Jan.) 1939.

129. Ingraham, N. R.: Complications Due to Arsenical Therapy in Syphilitic Pregnant Women, J. A. M. A. **112**:1537 (April 22) 1939.

130. Boon, T. H.: Aplastic Anemia with Complete Recovery, Brit. M. J. **2**:1041, 1938.

131. Osgood, E. E.; Riddle, M. C., and Mathews, T. J.: Aplastic Anemia Treated with Daily Transfusions and Intravenous Marrow: Case Report, Ann. Int. Med. **13**:357-367 (Aug.) 1939.

132. Heck, F. J., and Hall, B. E.: Leukemoid Reactions of the Myeloid Type, J. A. M. A. **112**:95 (Jan. 14) 1939.

resistance of the host, the site and extent of the infection and the reactivity of the bone marrow. These changes in the blood are seen most often in children. Diseases which may produce a similar hemopoietic response are specific blood dyscrasias, such as pernicious anemia, hemolytic anemia and polycythemia; hyperplasia of the bone marrow associated with acute hemorrhage or with any severe anemia, and, lastly, diseases involving the bone and bone marrow. Heck and Hall state that since there are a resemblance in the blood picture to that of leukemia and a leukemoid response, it is necessary to differentiate the conditions for purposes of treatment and prognosis.

Amidon [133] made careful hematologic studies in cases of acute infections. White blood cell counts, differential counts, filament-nonfilament counts and estimation of the toxic granulation of the polymorphonuclear neutrophils and of the vacuolization of the cytoplasm were done in 330 cases. After establishing his own criteria for mild, moderate, severe and grave infections, the author endeavors to evaluate the changes which occur with infection. He notes that in a series of 14 cases of appendicitis the filament-nonfilament index was altered in every instance; toxic granulation was observed in 73 per cent of the cases studied, and degenerative changes in the leukocytes were recorded in 43 per cent. Similar observations were made in cases of pneumonia and in a series of cases of miscellaneous infections.

In 39 cases of bacillary dysentery Ginsburg and his co-workers [134] observed a normal white cell count or mild leukocytosis. A "shift to the left" of the neutrophils was noted in 95 per cent of the cases. With recovery, the hematologic picture reverted to normal. Gezelius [135] studied the changes in the blood in 31 cases of rheumatic fever. It is his opinion that the occurrence and severity of the anemia are an accurate index of the activity of the disease. He also points out that the sedimentation rate parallels the severity of the anemia and that both the anemia and the sedimentation rate should be carefully followed to determine the course of the disease. It is also the opinion of Hubbard and McKee [136] that anemia is an indication of acute rheumatic fever.

Schmid [137] investigated the blood and bone marrow in cases of undulant fever. His observations led him to conclude that the changes

133. Amidon, E. L.: Hematologic Studies in Acute Infections, J. Lab. & Clin. Med. **24**:1009, 1939.

134. Ginsburg, H. M.; Hirschberg, E. M., and Brisker, F.: Bacillary Dysentery, J. A. M. A. **113**:1321 (Sept. 30) 1939.

135. Gezelius, G.: Die Anämie bei akuten rheumatischem Fieber im Kindesalter, Acta pædiat. **23**:361, 1939.

136. Hubbard, J. P., and McKee, M. H.: The Anemia of Rheumatic Fever, J. Pediat. **14**:66, 1939.

137. Schmid, N.: Blut und Knochenmark bei Morbus Bang, Schweiz. med. Wchnschr. **69**:191, 1939.

associated with undulant fever are similar to those observed in cases of typhoid fever. There is occasionally mild anemia. The white cells are usually reduced but occasionally normal in number. Lymphocytosis predominates, and often there is monocytosis. Associated with the neutropenia is a "shift to the left" of the polymorphonuclear neutrophils. The eosinophils are absent, and the platelets are unaltered. Studies of the blood in about 300 cases of brucellosis were also made by Calder and his associates.[138] Their results are similar to those of Schmid. These authors emphasize that this blood pattern is specific for Bang's disease.

The opinion of Vaizey and Clark-Kennedy [139] in regard to the anemia occurring with infections is most interesting. These authors point out that the early literature stated that dental sepsis is often considered the cause of anemia but that in the light of recent investigations there is little proof or evidence to support this view. Hemoglobin metabolism in the presence of chronic infection was studied by Vaughan and Saifi.[140] They noted a hyperplastic and not an aplastic marrow in association with the usual normocytic orthochromic anemia. Their studies on urobilinogen excretion gave no supportive evidence of an abnormal breakdown of hemoglobin. Porphyrin excretion was increased, and to the authors this suggested a disturbance in hemoglobin synthesis or degradation. In conclusion the authors state that this abnormality of hemoglobin synthesis is dependent on the presence of infection and is responsible for the anemia associated with a chronic septic process.

ANEMIA ASSOCIATED WITH CANCER

Although anemia has been identified for many years as a clinical aid in the diagnosis of cancer, the method of its production is not definitely known. The type of cancer, its site, the presence or absence of metastasis, the occurrence of bleeding and the questionable effect of a toxic cancerous agent on the bone marrow must all be included in considering the pathogenesis of the anemia. Various types of anemia have been described.

Monasterio [141] studied the morphologic and pathologic aspects of hemopoiesis in 33 cases of carcinoma of the stomach. Normocytic hypochromic anemia was the most common; less frequently normochromic anemia was observed, and rarely was hyperchromic anemia noted. The

138. Calder, R. M.; Steen, C., and Baker, L.: Blood Studies in Brucellosis, J. A. M. A. **112**:1893 (May 13) 1939.

139. Vaizey, J. M., and Clark-Kennedy, A. E.: Dental Sepsis in Relation to Anaemia, Dyspepsia, and Rheumatism, Brit. M. J. **1**:1269, 1939.

140. Vaughan, J. M., and Saifi, M. F.: Haemoglobin Metabolism in Chronic Infection, J. Path. & Bact. **49**:69, 1939.

141. Monasterio, G.: La sindrome anemica del carcinoma gastrico e sua patogenesi, Haematologica **20**:443, 1939.

bone marrow was normal in most instances but was occasionally hyperplastic. The author states that in some atypical cases megaloblasts and basophilic normoblasts were predominant in the bone marrow. He also describes the rare occurrence of plasma cells and histiocytes.

It is suggested by Liechti [142] that such secondary diseases as gastric cancer and tuberculosis, when present in a patient with known pernicious anemia, do not exaggerate the macrocytic anemia but rather alter the blood picture and produce microcytic anemia. This author points out that, since the hemopoietic changes often precede the clinical symptoms, patients with pernicious anemia should be carefully studied not only as regards relapse but for the occurrence of complications.

The pathogenesis of the anemia associated with gastric carcinoma was investigated by Schenken and his associates.[5] At autopsy the stomach showed a widespread neoplasm involving the entire prepyloric and pyloric areas; the entire mucosa was replaced by malignant tissue. There was no evidence of metastasis. An extract was prepared from the liver of the patient and given to a patient with pernicious anemia in relapse. No response was observed, although the patient subsequently responded to a similar extract prepared from the liver of a patient who died as a result of a cerebral hemorrhage. Apparently the patient with the gastric carcinoma was unable to produce any intrinsic factor, and consequently the liver was deprived of its reserve of erythropoietic maturing substance. This observation is certainly in agreement with the present conception of the physiology of hemopoiesis.

ANEMIA ASSOCIATED WITH ENDOCRINE DYSFUNCTION

A clinical investigation of the relation of the hemopoietic phenomena to endocrine disorders in women was made by Sharp and Mack.[143] Approximately 25 per cent of the 450 patients studied had anemia. In the group that had primary pituitary-thyroid disorders, including patients from the menarche to the age of 24, the blood usually showed normocytic anemia, and hypochromic anemia, was rare. Purpura was common and was often accompanied with a prolonged bleeding time. The platelets were normal or decreased in number. Women ranging in age from 25 to 39 were included in the group with "secondary thyro-ovarian failure." Hypochromic microcytic anemia was usually present. Thrombopenia and purpura were observed frequently. Other important characteristics were koilonychia, achlorhydria, dry skin, brittle hair, pallor, dysphagia and glossitis. In the last group, which included

142. Liechti, H.: Zweite Krankheit bei perniciöser Anämie, Schweiz. med. Wchnschr. **69**:172, 1939.

143. Sharp, E. A., and Mack, H. C.: The Relationship of Hemopoietic Phenomena to Endocrine Disorders in Women, Endocrinology **24**:202, 1939.

women from the age of 39 to the menopause, hypochromic microcytic anemia was predominant.

In summary, these authors point out that in 35.2 per cent of the 68 cases of anemia reported the condition occurred in women in the first group. They suggest that combined therapy be given for the glandular dyscrasia and the anemia as needed. In their opinion, since normocytic normochromic anemia occurs in younger persons and microcytic hypochromic anemia in the older age groups, the latter type of anemia is an evidence of chronicity.

The production of anemia by injections of pituitrin (solution of posterior pituitary extract) was reported by Dodds and Noble and reviewed in one of our previous articles. These investigators believe that the extract has a specific effect on the red blood cells. Gilman and Goodman [144] have verified the "pituitary anemia" but emphasize the fact that the substance injected alters the electrolytes in the plasma, with a subsequent change in the osmotic pressure and rupturing of the red blood cells. Dohan, Jeffers and Creskoff [145] have also noted anemia following the injection of extract of anterior pituitary in dogs. These authors, however, made no effort to explain the pathogenesis of the anemia.

The sternal marrow of normal persons and that of patients with hyperthyroidism and hypothyroidism were studied by Jones.[146] In the normal marrow approximately 6.2 per cent of the cells were nucleated, and the myeloid-erythroid ratio was 2:1 to 4:1. In the marrow from persons with hyperthyroidism there were 13.5 per cent of nucleated cells, and the myeloid-erythroid ratio was 5:1 to 20:1. Bone marrow from patients with myxedema revealed some atrophy. There were approximately 2.4 per cent of nucleated cells, and the myeloid-erythroid ratio was 1:1 to 3:1. Anemia was present in the 7 cases of myxedema investigated; there was no alteration in the blood of the 12 patients with hyperthyroidism. Microcytic, macrocytic and normocytic anemias occurred in the myxedematous group. The last-mentioned type was the most common. With adequate treatment the bone marrow returned to normal, and the anemia was eliminated. The hemopoietic changes observed appeared to parallel the increase in metabolism. The author believes that the thyroid gland has both a quantitative and a qualitative regulatory effect on the bone marrow.

144. Gilman, A., and Goodman, L.: Pituitrin Anemia, Nature, London **143**: 379, 1939.

145. Dohan, F. C.; Jeffers, W. A., and Creskoff, A. J.: Blood Pressure and Hematology in Dogs Injected with Anterior Pituitary Extract, Proc. Soc. Exper. Biol. & Med. **39**:327, 1938.

146. Jones, R. M.: Human Sternal Marrow in Hyperthyroid and Myxedematous States, Proc. Soc. Exper. Biol. & Med. **41**:55, 1939.

IRON DEFICIENCY

Iron Metabolism and Experimental Anemia.—The conditions under which iron may be absorbed from the alimentary tract continue to challenge investigation, particularly since the fundamental question of whether iron is received by the blood plasma and transported to certain tissues for storage irrespective of need or whether absorption of the metal is nicely adjusted to functional requirements has met varying replies from separate sources. Nevertheless, the conclusion seems warranted that the change in emphasis from investigations based on excreted iron to determination of the iron content of plasma and tissue oral administration of the mineral marks a significantly progressive step in the acquisition of facts concerning iron metabolism.

Continuing their studies on iron in the blood, Moore and his associates [147] selected as subjects 16 healthy young women with relatively constant levels of erythrocytes and hemoglobin. They found that individual variations of the content of the iron serum ranged throughout the day and during a six month period from extremes of 0.01 to 0.065 mg. per hundred cubic centimeters but that the changes followed no directional trend. With these normal subjects the values were unaffected by oral administration of liver or of medicinal iron. Studies of "nonhemoglobin blood iron" have been complicated by the presence of a fraction combined with the erythrocytes but dissociated from hemoglobin by the action of dilute acids or alkalis. The function of such "easily split-off" iron was not clearly understood until Barkan and Schales [148] demonstrated that this form of iron is probably derived from an intermediary compound formed during the breakdown of hemoglobin. Moore and his associates found that "easily split-off" iron varied in the same normal subject from 2.26 to 3.73 mg. per hundred cubic centimeters.

Moore and his co-workers [76] observed the changes in iron content of the serum following oral administration of the metal to dogs and to patients with differing forms of anemia. They determined that absorption of iron from the gastrointestinal tract leads directly to increase in serum iron and that no intermediate rise in the iron content of the lymph of the thoracic ducts can be observed. Furthermore, in dogs the concentration of iron in the serum is directly proportional to the size of the oral dose until the quantities given exert local toxic effects or induce changes in intestinal motility. Ferrous compounds soluble in water effect comparable increases of serum iron in patients with appropriate types of

147. Moore, C. V.; Minnich, V., and Welch, J.: Studies in Iron Transportation and Metabolism: III. The Normal Fluctuations of Serum and "Easily Split-Off" Blood Iron in Individual Subjects, J. Clin. Investigation **18**:543, 1939.

148. Barkan, G., and Schales, O.: Chemischer Aufbau und physiologische Bedeutung des "leicht abspaltbaren" Bluteisens: dreizehnte Mitteilung in der Reihe der Eisenstudien, Ztschr. f. physiol. Chem. **248**:96, 1937.

anemia, regardless of the degree of gastric acidity or its total absence. These authors also observed generally higher values for serum iron after administration of ferrous compounds than after its administration of iron in the trivalent form. The concomitant use of reducing agents, such as ascorbic acid and sodium formaldehyde sulfoxylate, appeared to enhance the absorption, as reflected by the serum iron, of both ferrous and ferric compounds, and this observation the authors interpret as further evidence that iron is absorbed largely, if not entirely, in the bivalent form. Bile pigment, chlorophyll and its derivatives, the secondary anemia fraction of liver and gastric mucin given in conjunction with iron failed to influence the subsequent serum increments of the metal. Of interest also is the demonstration by these authors of the apparently selective absorption of iron by patients with iron deficiency anemia as opposed to those with pernicious anemia, who already possess high concentrations of iron in the serum. It is the view of Moore and his colleagues that the hydrochloric acid of the stomach effects solution and ionization of iron salts and delays the subsequent formation in the intestine of insoluble and undissociated compounds. Furthermore, reducing substances in the intestine tend to retard the action of alkaline secretions in forming such physiologically inert iron compounds. Studies similar in scope are reported by Cosyns,[149] who gave ferrous and ferric salts containing equal amounts of iron to normal men and dogs and to pigs with nutritional anemia. He found that rises in the level of serum iron followed oral administration of ferrous compounds, whereas administration of the trivalent form of the metal led to little if any evidence of absorption.

Hemmeler [150] also has reported results of determinations of serum iron concentration. He found for healthy men a range of 100 to 130 micrograms of iron per hundred cubic centimeters and for menstruating women a range of 80 to 100 micrograms, but the values for nonmenstruating women equaled those for men. He determined the level of serum iron in cases of various types of anemia and found low values, such as 38 micrograms per hundred cubic centimeters, in cases of achylic chloranemia and high levels, such as 218 micrograms per hundred cubic centimeters, in cases of pernicious anemia. Appropriate therapy resulted in normal values for serum iron. On the basis of his observations of serum iron in conditions associated with jaundice Hemmeler concluded that the liver plays an important part in the secretion of iron and that its role in the mechanism of regulation of iron is more important than that of the intestine.

149. Cosyns, H.: Etude comparée des courbes de résorption des sels ferreux et des sels ferriques, Compt. rend. Soc. de biol. **130**:786, 1939.

150. Hemmeler, G.: Serumeisen und Eisentherapie, Schweiz. med. Wchnschr. **69**:316, 1939; Serumeisen und Leber, Klin. Wchnschr. **18**:1245, 1939.

An investigation by Jenkins and Thomson [151] of what they designate as nonhemoglobin cellular iron included 110 determinations in 24 cases of anemia. One might assume that the fraction with which they were concerned is identical with the "easily split-off" iron of Barkan, but their method for its estimation, involving determinations of the total iron content of the blood and subtraction from this figure of the calculated amount of hemoglobin iron based on a colorimetric hemoglobin determination, is open to several serious objections. Their results indicate that the "nonhemoglobin cellular iron" represents from 7 to 49 per cent of the total iron content of blood, the higher values occurring in the presence of severe anemia. This finding is attributed by the authors to a hypothetic compensatory mechanism which retains erythrocytes in the circulation beyond their normal span of survival, with consequent breakdown of some of the hemoglobin to intermediate iron-containing compounds.

The older view of a specific iron excretory function of the colon, which has been largely disestablished by the work of Widdowson and McCance and others, was reinvestigated by Maddock and Heath.[152] They performed colonic explants on the abdominal walls of 4 dogs and administered iron by mouth and by injection to these animals and to others, which had not been operated on. They obtained no evidence by histologic examination and qualitative tests for iron that the metal can be observed in process of excretion by any part of the alimentary tract in situ or by colonic explant. Their work supports the view that whatever iron may be excreted by the bowel is an extremely small amount.

More extensive studies of the behavior of radioactive iron are reported by Hahn and his associates [153] and by Manwaring.[154] Employing standardized anemic dogs, Hahn and his group ascertained that the need for iron determines its absorption, so that under ordinary circumstances the requirement for excretion is explicably small. However, they fail to share the view that absorption of iron depends on differences in gradient between intestinal concentrations and plasma or lymph concentrations of the metal. They agree that iron is transported by the plasma, and they report detection of radioactive iron in circulating erythrocytes in an almost incredibly short time, amounting in some instances to but a few hours after absorption. Such iron is also found in mobilizable form in the liver, spleen and bone marrow. In the same

151. Jenkins, C. E., and Thomson, M. L.: The Non-Haemoglobin Cellular Iron in Anaemia, Brit. J. Exper. Path. **19**:417, 1938.

152. Maddock, S., and Heath, C. W.: Is Iron Excreted by the Gastro-Intestinal Tract of the Dog? Arch. Int. Med. **63**:584 (March) 1939.

153. Hahn, P. F.; Bale, W. F.; Lawrence, E. O., and Whipple, G. H.: Radioactive Iron and Its Metabolism in Anemia, J. Exper. Med. **69**:739, 1939.

154. Manwaring, W. H.: Metabolism of Radioactive Iron, California & West Med. **51**:293, 1939.

laboratory [155] radioactive "labeled" iron (the radioactive portion forms an infinitesimal fraction of the total dose) was injected intravenously into dogs in the form of ferrous gluconate. The initial extra output in urine and feces during a period of three to fifteen days ranged from 2 per cent to 8 per cent of the iron injected. For an indefinite period after intravenous administration of 100 to 250 mg. the feces contained measurable amounts of radioactive "labeled" iron varying from 0.05 to 0.4 mg. per day. Destruction of erythrocytes by acetylphenylhydrazine caused a definite increase in the "labeled" iron eliminated in the feces, probably through the increased iron content of the bile. In dogs the bile usually contributes very little iron to the intestinal contents (about 0.01 mg. per day). The Rochester investigators conclude that the body controls its iron stores by absorption or lack of it rather than by its capacity to eliminate the metal. The dog excretes iron with difficulty and in small amounts, even in the plethoric state, by means of the biliary and gastrointestinal tracts.

Hahn and Whipple [156] were able to limit the production of hemoglobin by their standardized dogs by means of restriction of dietary protein, even when excessive amounts of iron were given by mouth and by vein. They found that under the stress of protein limitation the proteins of salmon muscle, banana and carrot were well utilized and that the ratio of dietary protein to hemoglobin production was 7 or 8 Gm. to 1 Gm. Whipple and Robscheit-Robbins [157] observed the effect of spontaneous nephritis on the hemoglobin production of anemic dogs. In the early stages of the disease little or no effect is manifest. During more advanced nephritis there may be no change or a moderate decrease in production of hemoglobin. In such cases the average amounts to 70 per cent of the normal production. They conclude that spontaneous anemia in the nephritic dog cannot be expected to result from this degree of impairment of hemoglobin production.

Using Whipple's method of preparing anemic and iron-depleted dogs by repeated bleeding, Wigodsky and his collaborators [158] found that commerical preparations of gastric mucin stimulated production of hemoglobin by amounts 55 to 70 per cent greater than could be accounted for by the quantities of iron present in the preparation.

155. Hahn, P. F.; Bale, W. F.; Hettig, R. A.; Kamen, M. D., and Whipple, G. H.: Radioactive Iron and Its Excretion in Urine, Bile, and Feces, J. Exper. Med. **70**:443, 1939.

156. Hahn, P. F., and Whipple, G. H.: Hemoglobin Production in Anemia Limited by Low Protein Intake, J. Exper. Med. **69**:315, 1939.

157. Whipple, G. H., and Robscheit-Robbins, F. S.: Nephritis and Its Influence upon Hemoglobin Production in Experimental Anemia, J. Exper. Med. **69**:485, 1939.

158. Wigodsky, H. S.; Bussabarger, R. A., and Fogelson, S. J.: The Effect of Gastric Mucin on the Hemoglobin Regeneration in Anemic Dogs, J. Lab. & Clin. Med. **25**:13, 1939.

Gastric mucin, however, in their studies was not as effective a stimulus to new hemoglobin formation as was beef liver.

Fouts and his associates [159] produced hypochromic and microcytic anemia in 3 adult dogs by means of diets lacking in factor I, believed to be identical with vitamin B_6, or the rat antidermatitis factor. The anemia was not relieved by iron but was cured by the addition of crystalline factor I. These observations are believed by the authors to confirm their earlier conclusion that the antianemia factor of dogs and the antidermatitis factor of rats are identical.

Guerrant and Hogan [160] induced milk anemia in growing rats and subsequently fed the animals diets containing deaminized casein. The anemia persisted and could not be relieved by supplements of individual essential amino acids. Of the proteins examined, casein proved to be the most potent source of the antianemia agent. Lactalbumin and corn and wheat gluten were relatively ineffective. Corner [161] reported additional observations on the pine disease (cobalt deficiency anemia) prevalent among sheep and cattle in certain parts of Scotland. He found that 1 mg. of cobalt daily for fourteen days cures the disease in sheep and prevents its recurrence for at least six months. Latsky [162] confirmed the work of the Wisconsin investigators on the importance of copper as a supplement to iron in the treatment of milk anemia of growing rats. He was able to obtain reproduction of rats receiving a milk diet supplemented only by iron and copper.

Hypochromic Anemia of Adults.—Anemia dependent on bleeding peptic ulcer has received a considerable amount of attention in respect to rate of blood regeneration, because it is unique among hypochromic anemias in its high incidence, its known and remediable causation and the opportunities for its prolonged observation under strict dietary and medicinal management. Lyons and Brenner [163] have reviewed the records of 237 cases observed at the Peter Bent Brigham Hospital between 1913 and 1936. Values for hemoglobin were not considered, but the weekly rate of erythropoiesis was determined in 177 cases on the basis of the lowest erythrocyte count. Apparently, speed of regen-

159. Fouts, P. J.; Helmer, O. M., and Lepkovsky, S.: Cure of Microcytic Hypochromic Anemia in Dogs with Crystalline "Factor I," Proc. Soc. Exper. Biol. & Med. **40**:4, 1939.

160. Guerrant, R. E., and Hogan, A. G.: Effect of Amino Acids on Anemia Caused by Deaminized Casein, J. Biol. Chem. **128**:363, 1939.

161. Corner, H. H.: Cobalt as a Factor in the Control of Nutritional Anaemia, Brit. M. J. **2**:169, 1939.

162. Latsky, J. M.: Haematological Studies in Nutrition, South African M. J. **13**:461, 1939.

163. Lyons, R. H., and Brenner, C.: Erythropoiesis Following Bleeding Peptic Ulcer, Am. J. M. Sc. **198**:492, 1939.

eration depended on the current degree of anemia present, regardless of the duration of the illness or the initial severity of the anemia. The rate of increase of erythrocytes in their cases, in which the patients were treated for the most part by a Sippy regimen, equaled that reported for patients receiving a liberal puréed diet and iron (Meulengracht; Schmid). The authors also came to the conclusion, held by some others, that beyond the actual increment of donated cells transfusion appeared to have no effect on the rate of erythropoiesis. In comment, it may be pointed out that a fallacy is involved in grouping patients with bleeding peptic ulcer without careful analysis of the case history and the nature of the anemia, since the extent of depletion of iron and other materials required for blood formation, depending largely on the duration of bleeding, may be expected to influence the rate of formation of red blood cells.

Pohle and Heath [164] report that administration by mouth of acid and alkaline salts to patients with hypochromic anemia treated by parenteral administration of iron failed to influence the rate of regeneration of hemoglobin, although changes in plasma volume were induced by altering the hydrogen ion concentration of the blood. They obtained an average of 70 per cent utilization of iron injected intramuscularly in new hemoglobin formation.

Determinations of the ascorbic acid content of the blood plasma were made by Alt, Chinn and Farmer [165] for 44 patients with achlorhydria associated with pernicious anemia or iron deficiency anemia. In the case of persons whose dietary histories indicated adequate intake of vitamin C, the ascorbic acid content of the blood was decreased from 0.87 mg. per hundred cubic centimeters, the average for normal persons, to 0.57 mg., the average for patients with pernicious anemia. When the diet had been deficient in vitamin C the value for normal persons was 0.64 mg., for persons with pernicious anemia 0.47 mg. and for those with iron deficiency anemia 0.45 mg. per hundred cubic centimeters. The authors suggest various factors to which these relatively low values may be attributed, namely, destruction of vitamin C in alkaline gastric juice, destruction by bacteria and malabsorption.

Five cases of hypochromic anemia occurring in men are reported by Thiele.[166] The age range was 14 to 49 years. Two of the patients

164. Pohle, F. J., and Heath, C. W.: The Influence of Acid and Alkaline Salts upon the Blood in Hypochromic Anemia Treated by Iron Parenterally, Am. J. M. Sc. **197**:437, 1939.

165. Alt, H. L.; Chinn, H., and Farmer, C. J.: The Blood Plasma Ascorbic Acid in Patients with Achlorhydria (Pernicious and Iron Deficiency Anemia), Am. J. M. Sc. **197**:229, 1939.

166. Thiele, W.: Ueber Anämien vom Typ der essentiellen Hypochromanämie bei Männern, Deutsche med. Wchnschr. **65**:208, 1939.

had complete anacidity. In all cases a history was obtained of rickets in childhood, or osseous deformities suggestive of infantile rickets were apparent. The author suggests that deficient mineral endowment before birth may play a part in the subsequent development of both rickets and iron deficiency anemia. Two cases of achlorhydric hypochromic anemia associated with peripheral neuritis are reported by Worster-Drought and Shafar.[48] In 1 the patient was a man of 74 whose anemia was attributed to bleeding hemorrhoids, and in the other the patient was a woman of 51 in whom the condition followed partial gastric resection for ulcer of the stomach. The authors report that the objective neurologic findings improved after iron therapy and recovery from the anemia, but the possible influence of a deficiency of the vitamin B complex does not appear to have been sufficiently considered.

Changes in the blood following operations on the stomach were observed by Fravi [167] and by Dreher.[168] The former found 16 instances of anemia, primarily hypochromic, among 50 patients who had undergone various degrees of resection of the stomach. The latter author reports the hematologic values in 101 cases two to eleven years after partial gastric resection. Of these, the erythrocyte count was less than 4,500,000 per cubic millimeter in 50 cases, and the color index was greater than 1 in 60 cases and below 1 in 29. In 40 cases the mean diameter of the erythrocytes was above 7.8 microns, and in 60 the reticulocyte percentage was above 5. Thirteen patients were found to have anemia associated with an increased red cell diameter, a high color index and an elevated reticulocyte percentage. The syndrome, including anemia, frequently resulting from removal of parts or all of the stomach is reviewed from both clinical and experimental points of view by Leroux and Vermes.[52] The authors emphasize the relation between gastroduodenal function and hemopoiesis.

In a discussion of the treatment of iron deficiency anemia, Fowler and Barer [169] conclude that administration of inorganic ferrous compounds is preferable to the use of other iron preparations. So far as effect on hemopoiesis is concerned, they find no indications for the employment of such supplements to medicinal iron as extracts of liver, vitamins or other metals. Similar conclusions are arrived at by Whitby.[170] In discussing the mechanism of production of iron defi-

167. Fravi, G. G.: Ueber Sekretions- und Blutveränderungen nach Magenoperationen, Schweiz. med. Wchnschr. **69**:174, 1939.

168. Dreher, M.: Veränderungen des roten Blutbildes nach Magenresektion, Ztschr. f. klin. Med. **136**:525, 1939.

169. Fowler, W. M., and Barer, A. P.: The Treatment of Iron Deficiency Anemias, J. A. M. A. **112**:110 (Jan. 14) 1939.

170. Whitby, L. E. N.: Advances in Anaemia and Blood Diseases, Practitioner **143**:391, 1939.

ciency, Delachaux [171] emphasizes the importance of digestive disturbances leading to impaired absorption of iron and failure to utilize iron after its absorption. When the latter condition is present the author believes that liver extracts, manganese and copper may be of value.

Nutritional Anemia of Children.—The subject of iron metabolism in infancy has been reviewed by Wallgren,[172] who also reports his own studies on balance, carried out during the first year of life with infants born prematurely. He concludes that the anemia of premature infants, prevalent during the first two or three months, results from increased destruction of blood and is not related to iron deficiency. He found no evidence of functional incapacity of the marrow in such cases, except possibly a relative one due to the demands incident to rapid increase of blood volume. The need for new blood with its associated demands for blood-forming materials, especially iron, is responsible in large part for the lower values for erythrocytes and hemoglobin which persist in the case of premature infants after the period of postfetal hemolysis. But also of importance, according to the author, are the effects of exogenous factors on utilization of blood-building substances. Such factors, especially common among premature babies, include dietary errors and infections.

Josephs [173] studied the intake and output of iron of normal infants and found evidence of approximately 60 per cent absorption of dietary iron. Retention was decreased during infections and in infants not receiving vitamin D. The influence of infection may, however, be attributed to diminished intake of food. Josephs found that retention of iron tends to be above the average in cases of anemia even when the level of hemoglobin is falling, an observation which appears to be opposed to the usual concept of iron deficiency anemia and suggested to the author that "avidity of the tissues for iron might be a factor in the production of anemia." It is concluded that availability of tissue iron is important in the consideration of iron deficiency as a cause of anemia.

In a study of the utilization of medicinal iron, Josephs [174] found that retention was enhanced when the daily intake exceeded 2 mg. per kilogram of body weight. The iron balance became negative when the total amount taken into the alimentary tract was approximately 0.1 mg.

171. Delachaux, A.: Remarques au sujet de la conduite thérapeutique dans les anémies par manque de fer, Rev. méd. de la Suisse Rom. **59**:278, 1939.

172. Wallgren, A.: Le fer dans la nutrition de l'enfant. Recherches sur le métabolisme du fer chez les enfants prématurés, nourris au sein, pendant la première année de leur existence, Rev. franç. de pédiat. **15**:117, 1939.

173. Josephs, H. W.: Iron Metabolism in Infancy: I. Factors Influencing Iron Retention on Ordinary Diets, Bull. Johns Hopkins Hosp. **65**:145, 1939.

174. Josephs, H. W.: Iron Metabolism in Infancy: II. The Retention and Utilization of Medicinal Iron, Bull. Johns Hopkins Hosp. **65**:167, 1939.

per kilogram per day. Greater retention of medicinal iron occurred in anemic infants than in those with a normal blood picture. Supplementary administration of copper appeared to increase the total utilization of medicinal iron but had little effect on the rate of utilization; it exerted no influence on retention of iron. For several days after institution of iron therapy, storage of the metal preceded its utilization. In anemic infants the percentage of retained iron utilized for hemoglobin production varied inversely with the amount retained. When 2 mg. or less per kilogram per day was retained the utilization was approximately 100 per cent. The author compares this to the high degree of utilization of injected iron, which he attributes to a dose of less than 2 mg. per kilogram.

According to Josèphs, after a period of medicinal iron therapy the increase in hemoglobin continues for about two to three weeks, and then the values remain stationary even though all the retained iron has not been used and the level of hemoglobin has not attained normal limits. He concludes that medicinal iron possesses an important regulatory function in iron metabolism and erythropoiesis apart from its role as a "building store" for hemoglobin.

The possible relation of lowered secretion of acid by the stomach to the nutritional anemia of infants and young children has been studied by Wilson.[175] In 12 cases of hypochromic anemia in young children he found 8 children with achlorhydria and 4 with hypochlorhydria after stimulation with alcohol or histamine. Treatment with hydrochloric acid, 1 to 2 cc. of a 10 per cent solution every four hours for seven to fourteen days, failed to elicit a reticulocyte response. Good therapeutic results were obtained from administration of iron as ferrous sulfate in a dose ranging from 0.65 to 2 Gm. daily.

The value of a concentrated syrup made from cane sugar has been emphasized by Wilbar[176] in discussing the prevention of nutritional anemia in infants. He found an average value for hemoglobin for 242 children residing on a sugar plantation in Hawaii of 9.8 Gm. per hundred cubic centimeters in 1936. Subsequently (in 1938), after the molasses supplement had been used, the average value for hemoglobin was 12.6 Gm. The cane sugar syrup contained iron ranging from 1 to 3 mg., and copper averaging 0.2 mg., per hundred cubic centimeters. The relatively high value for copper may be attributed to the preparation and concentration of the syrup in copper kettles. As a more or less complete dietary adjunct to milk in the feeding of young infants,

175. Wilson, R.: The Relation of Achlorhydria to the Nutritional Anaemia of Children, Canad. M. A. J. **41**:176, 1939.

176. Wilbar, C. L., Jr.: A New Carbohydrate for Prevention of Nutritional Anemia in Infants: Preliminary Report, Am. J. Dis. Child. **58**:45 (July) 1939.

Takuma and Sakurai [177] advocate soy bean meal. The product is a rich source of protein and in this respect compares favorably with casein, possessing a high content of the essential amino acids tryptophan and histidine. It also contains unsaturated fat and vitamins A and D and is especially well suppled with the B complex. Furthermore, soy bean meal is relatively rich in iron and copper. Infants with nutritional anemia improved rapidly when soy bean meal was added to the diet in amounts of 26 to 42 Gm. daily for the age group between 1 and 10 months and in quantities between 400 and 600 Gm. daily for older children. According to Lesné and Briskas,[178] mobilization of tissue iron is facilitated by administration of copper salts.

Hutchison [179] studied 300 infants in the first year of life. He found abnormally low values for hemoglobin in 26 per cent of breast-fed infants and in 35 per cent of those receiving cow's milk formulas. He concluded that the important etiologic factors of the nutritional anemia of infancy are undue prolongation of an exclusive milk diet, low birth weight and persistent infection. As a preventive measure he recommends administration of iron and ammonium citrates, 0.3 to 0.6 Gm. daily, or the use of diet supplements to which iron has been added. Eight hundred and eighty-three rural school children in Florida were examined by Abbott and Ahmann,[180] who found hemoglobin levels of less than 9.64 Gm. per hundred cubic centimeters in 50 per cent. An additional 31 per cent had concentrations below 11.7 Gm. Iron and ammonium citrates, 1 Gm. three times a day, gave good results in spite of inadequate diet or hookworm infestation. Diets well supplied with foods high in iron content failed to influence subnormal values for hemoglobin after ninety days of use.

The subject of nutritional anemia of infancy and childhood has been reviewed by Smallwood [181] and by Moore.[182] The latter emphasizes the value of the ferrous salts of iron and advocates their use without copper or liver fraction supplements. Parenteral administration of iron is recommended only in cases of persistent diarrhea.

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177. Takuma, T., and Sakurai, K.: Ueber die blutbildende Wirkung des Sojamehls, Monatschr. f. Kinderh. **79**:62, 1939.

178. Lesné, E., and Briskas, S. B.: Le traitement cuprique des anémies par carence alimentaire chez le nourrisson, Médecine **19**:618, 1938.

179. Hutchison, J. H.: Nutritional Anaemia in Industrial District, Arch. Dis. Childhood **13**:355, 1938.

180. Abbott, O. D., and Ahmann, C. F.: Iron Deficiency Anemia in Children, Am. J. Dis. Child. **58**:811 (Oct.) 1939.

181. Smallwood, W. C.: The Anaemias of Infancy and Childhood, Practitioner **142**:453, 1939.

182. Moore, C. V.: Nutritional Anemias of Infancy and Early Childhood, Ohio State M. J. **35**:25, 1939.

Anemia of Pregnancy.—An understanding of the physiologic variations of the blood in pregnancy is essential to accurate analysis and interpretation of pathologic observations. As yet, however, such knowledge is decidedly incomplete. A number of studies have been recently reported of the changes occurring in the blood in apparently healthy pregnant women. Unfortunately, however, some of the work is open to question because of apparent technical errors and inaccurate calibration in the measuring of hemoglobin.

The hematologic values for 1,000 private obstetric patients are reported by Eskridge and Serwer.[183] The data are difficult to interpret because of the method of presentation, but the lowest range of erythrocyte counts was between 3,000,000 and 3,500,000 per cubic millimeter and represented, apparently, 5.1 per cent of the patients observed during the first trimester, 7.8 per cent during the second trimester and 16.4 per cent during the last three months of gestation. The lowest range of hemoglobin levels was between 10.2 and 11.9 Gm. per hundred cubic centimeters and represented 15.8 per cent of the patients in the first trimester, 15.5 per cent in the second and 38.0 per cent in the third. However, the values for hemoglobin appear to be generally too high in comparison with the erythrocyte counts, possibly because of the use of inaccurate calibration in an older method of determination.

The effect of pregnancy on the blood picture was studied by Kenyon and Macy,[184] who observed hourly physiologic variations in the counts. Many of their erythrocyte counts are, however, inexplicably low. Sternal marrow was aspirated from pregnant and nonpregnant women by Pitts and Packham.[185] Nucleated cell counts and differential counts were made, but the practice of the authors of removing 10 cc. of so-called marrow leads to inclusion of such a disproportionate amount of circulating blood, probably at least 99 per cent, that quantitative statements concerning the composition of the marrow are open to question. The hematologic values for 525 pregnant women were determined by Gottlieb and Strean.[186] Of these, 275 received no antianemia therapy, and 250 were given various preparations of iron. The blood of the infants was studied in 100 cases. Among the untreated patients the average values for hemoglobin during the three trimesters were respectively

183. Eskridge, J. B., Jr., and Serwer, M. J.: Blood Studies in Private Obstetrical Patients, South. M. J. **32**:24, 1939.

184. Kenyon, F., and Macy, I. G.: Hourly Physiologic Variations in Peripheral Hemoglobin, Red and White Counts of Women: Effect of Pregnancy upon Blood Counts, Human Biol. **10**:511, 1938.

185. Pitts, H., and Packham, E. A.: Hematology of Sternal Marrow and Venous Blood of Pregnant and of Non-Pregnant Women, Arch. Int. Med. **64**:471 (Sept.) 1939.

186. Gottlieb, R., and Strean, G. J.: The Prevention of Maternal and Infant Anemia, Surg., Gynec. & Obst. **68**:869, 1939.

11.2 Gm., 10.5 Gm. and 9.1 Gm. per hundred cubic centimeters. A similar decline in the level of hemoglobin did not occur in the iron-treated group. Iron and ammonium citrates, reduced iron, ferrous sulfate with vitamin B complex and ferrous carbonate with copper were employed. All yielded good results, and no advantage seemed to attend the use of the two last-named, "supplemented" preparations. The authors made the interesting observation that the infants of untreated mothers at birth possessed an average erythrocyte level of 7,000,000 per hundred cubic centimeters and a hemoglobin concentration of 16.8 Gm. whereas the values for infants of the treated group were, respectively, 5,290,000 per cubic millimeter and 15.44 Gm. However, after thirty-two weeks the average red cell count for the infants of untreated mothers was 2,860,000 per cubic millimeter, and the hemoglobin content averaged 7.14 Gm., whereas the respective values for the infants of mothers who had received medicinal iron during gestation were 4,300,000 per cubic millimeter and 11.48 Gm.

A study of the effect of administration of iron on the level of hemoglobin during pregnancy was carried out by Widdowson.[187] Hemoglobin estimations only were done. The progressive decline which characterized the values for hemoglobin in her cases was converted into a rise by administration of either reduced iron or iron and ammonium citrates. However, after withdrawal of iron the values for hemoglobin fell at approximately the rate observed before institution of iron therapy. According to the author's previously expressed views on iron absorption and excretion, an excess of the metal should have been stored during the period of its administration. Failure of utilization of such stored iron is attributed by her to lack of stimulus to the marrow, and she believes that such incitement to hemopoietic activity may depend on high values for plasma iron. However, in the absence of erythrocyte counts and determinations of cell volume, interpretation of Widdowson's data is difficult.

Standards for normal minimal values during pregnancy have been set by Labate [188] at 4,000,000 per cubic millimeter for erythrocytes and 11.6 Gm. for hemoglobin. According to these criteria, he found a 48 per cent incidence of anemia among 881 pregnant women. The prevalence of anemia of the macrocytic type was notable. Dietary deficiencies appeared to exert an especially great effect on the blood picture in cases of prenatal complications. Three hundred and twenty-five of Labate's patients were given ferrous sulfate, 0.32 Gm. three times a day. At delivery the average erythrocyte count was 4,090,000 per

187. Widdowson, E. M.: Iron Administration and Haemoglobin Levels During Pregnancy, Lancet **2**:640, 1939.

188. Labate, J. S.: Classification and Treatment of Anemias of Pregnancy, Am. J. Obst. & Gynec. **38**:48, 1939.

cubic millimeter, and the average value for hemoglobin, 11.61 Gm. Three hundred and seven women were not given iron, and at delivery the average values for red cells and hemoglobin were respectively 3,010,000 per cubic millimeter and 8.16 Gm. Labate found a morbidity rate of 14.8 per cent among the treated patients as compared to a rate of 19.5 per cent in the untreated group. He concludes that "iron therapy must be continued beyond the period of hospital stay to have any significant effect on the erythrocytes and hemoglobin of the postpartum anemic patient."

Hemoglobin estimations and erythrocyte counts were done in the cases of 88 pregnant women at monthly intervals or oftener by Bourdillon and his associates.[189] The patients were divided arbitrarily into two groups, and to the members of one was given iron and ammonium citrates, 4 Gm. daily, whereas those of the other were untreated. An average decline in the concentration of hemoglobin from the fifth to the ninth month of 0.7 Gm. per hundred cubic centimeters occurred in the untreated group, and an average increase of 1.15 Gm. was observed among those receiving iron. The authors state in respect to their cases that "multiple pregnancies, age, and poverty were all associated with a low hemoglobin, but which, if any, was the dominant factor could not be determined."

Tentative standards of normality for the blood in pregnancy were formulated by Bethell, Gardiner and MacKinnon.[190] The mean and minimum levels were based on data obtained at monthly intervals during gestation from 30 women. The criterion for selection of the cases was return in each instance to the normal range of values for nonpregnant women at the seventh week after delivery in the absence of antianemia therapy or change in dietary habits. The minimum normal values adopted for nonpregnant women were: erythrocytes, 4,130,000 per cubic millimeter, hemoglobin, 12.17 Gm., and packed cell volume, 37.5 per cent. All determinations were made in duplicate with oxalated venous blood, with certified instruments and standardized methods. The lowest values were found at the beginning of the seventh month, when the red cell count sometimes fell to a level of 3,500,000 per cubic millimeter and the hemoglobin content to 10.1 Gm. The authors were unable to attribute the physiologic decline in values during pregnancy solely to dilution of the plasma, since during the first trimester of pregnancy a uniform decrease in the mean corpuscular hemoglobin was observed and in the second trimester an increase in the mean corpuscular volume was noted. On the basis of such standards of normality an

189. Bourdillon, J. F.; Cargill, D. R.; Cosh, J., and Miles, J. A. R.: Mild Anaemias in Pregnancy, St. Thomas's Hosp. Rep. **3**:89, 1938.

190. Bethell, F. H.; Gardiner, S. H., and MacKinnon, F.: The Influence of Iron and Diet on the Blood in Pregnancy, Ann. Int. Med. **13**:91, 1939.

incidence of 53.8 per cent of true anemia was observed in 158 clinical cases studied. In 26 per cent the anemia was hypochromic and either normocytic or microcytic; in 15.2 per cent it was orthochromic and macrocytic, and in 12 per cent it was hypochromic and macrocytic. Anemia in the first group was attributed solely to iron deficiency; in the second group it was attributed to dietary deficiencies related to inadequate intake of animal protein, and in the third group it was ascribed to a lack of both iron and protein. In a controlled series of clinical studies it was found that administration of ferrous sulfate alone in a dose of 0.32 Gm. three times a day corrected anemia due to iron deficiency; improvement of the diet led to a satisfactory hemopoietic response in cases of nutritional deficiency, but the most satisfactory results were obtained in the latter group when institution of a diet adequate in protein was combined with administration of medicinal iron. It was also found that iron therapy given to a group of women with a presumably normal blood picture led to higher levels of hemoglobin after delivery than were observed in a group of untreated women with the same initial values.

Cases of pernicious anemia of pregnancy are reported by Dor,[191] Onhauser and Mitchell[64] and Ritter and Crocker.[192] The last-named authors describe a case of severe macrocytic anemia of pregnancy with suboptimal response to parenteral liver extract and the subsequent development of a similar macrocytic anemia in the infant. After delivery the blood of the mother returned to normal, and the infant gradually recovered, although not demonstrably as the result of administration of liver extract, medicinal iron or vitamin C.

A case of erythroblastic splenomegaly occurring in a young Negress during pregnancy was reported by Moore and Pastore.[120] At autopsy extramedullary erythropoiesis was observed, but the bone marrow was said to be normal. No explanation was given for the disturbance in erythrogenic tissue except the suggestion that it may have followed one of the commoner forms of anemia of pregnancy.

An experimental study of the effect of maternal diet supplements on the size of the erythrocytes of newborn rats was carried out by Briese and Higgins.[193] Twenty per cent (by weight) of desiccated hog stomach (ventriculin) was added to the standard ration for varying periods during gestation. The size of the red cells was determined by measur-

191. Dor, P.: L'anémie pernicieuse gravidique; réflexions à propos de deux observations, Bull. méd., Paris **53**:571, 1939.

192. Ritter, J. A., and Crocker, W. J.: Macrocytic Anemia of Pregnancy and Anemia of the Newborn, Am. J. Obst. & Gynec. **38**:239, 1939.

193. Briese, E., and Higgins, G. M.: The Effect of Feeding Ventriculin to Pregnant Rats, with Special Reference to the Size of the Red Blood Cells of the Young, Anat. Rec. **73**:105, 1939.

ing the diameters of 100 cells from each sample. A total of 177 control rats was used, the offspring of mothers on standard unsupplemented diets, and the mean erythrocytic diameter was found to be 9.42 microns. One hundred and twenty-five newborn test rats were examined, and in general it was found that the litters of the mothers who had received ventriculin possessed red cells with smaller diameters than those of the controls. However, the range of results was wide. The authors conclude that maturation of the blood cells in the developing fetus is usually accelerated by addition of ventriculin to the maternal diet.

POISONING BY PHYSICAL AGENTS

Lead.—To throw some light on the value of the "basophilic aggregation test" of infants as an evidence of lead poisoning, McCord and Bradley [194] studied the percentage of red blood cells showing this phenomenon in newborn animals and human beings. In the albino rat 71.7 per cent of the cells showed basophilic aggregations at birth, and in infants, 5.3 per cent revealed the same phenomenon. In the case of the latter the number diminished rapidly, reaching a level of 0.5 to 2.0 per cent by the eighth day. Thus, beyond ten days an increase in the number of cells showing basophilia is of pathologic significance in infants. In young rats, however, a high percentage of erythrocytes containing basophilic substance persists until near the hundredth day of life, militating against the use of these animals in studying experimental lead poisoning.

In Gocher's [195] study of lead workers, he found that a count of over 2 stipple cells per 2,000 red blood cells indicates toxicity and absorption, the count being higher with the greater degrees of toxicity. With the variations in the cycle of lead excretion, stipple cells may appear or disappear from the circulation. Anemia may be absent (over 90 per cent [Sahli] hemoglobin) in cases of severe poisoning. Usually, when there is poisoning the reading is 68 per cent or less. When there is involvement of the liver the readings are usually from 65 to 70 per cent. Reticulocytes decrease in number with lessened exposures to lead, rising when the hygiene is faulty. The number is increased in patients with abdominal cramps and involvement of the nerves and in patients with impending toxemia from lead poisoning. The behavior of the reticulocytes seems to be independent of the stipple cells. A case of a man in apparently perfect health with 100 per cent reticulocytes is recorded.

194. McCord, C. P., and Bradley, W. H.: Basophilic Aggregations in Blood of Newly Born: (*a*) Laboratory Animals; (*b*) Humans, Am. J. Clin. Path. **9**: 329, 1939.

195. Gocher, T. E. P.: Blood Examinations in Lead Poisoning, Northwest Med. **38**:289 (Aug.) 1939.

The conditions present in early susceptibility to lead are summarized as follows: 1. An increase in reticulocytes occurs in all cases. 2. An increase in stipple cells occurs in about 25 per cent of the cases. 3. A slight drop in diastolic pressure has been observed in 15 cases of "cramps." 4. The hemoglobin percentage and the number of red blood cells are usually not affected. 5. There is slight leukocytosis, with a count of about 10,000 per cubic millimeter in most cases. 6. At first there is an increase in neutrophils, to about 88 per cent at times. 7. There is an increase in large mononuclear cells, to 10 or 12 per cent. 8. There is an initial increase in eosinophils, to 4 to 10 per cent, and then a decrease occurs. 9. Polychromatophilia is present in varying proportions in the red cells. The blood picture and general health of patients suffering from lead poisoning were found by Holmes, Campbell and Amberg [196] to improve rapidly after daily ingestion of 100 to 200 mg. of vitamin C. The stipple cells disappeared from the blood stream, and the urinary excretion of lead was reduced to normal limits.

Tompsett and Anderson [197] conclude that excretion of more than 100 micrograms of lead per hundred cubic centimeters of blood, or a total daily excretion of 1 mg. or more, is indicative of lead poisoning. In rabbits made anemic by prolonged injection of lead salts, Lourau, de Sacy and Arthus [198] found that blood regeneration could be stimulated by injection of liver extracts which were active in the treatment of pernicious anemia.

Benzene.—Erf and Rhoads [199] reported the changes in the blood of 9 patients with benzene poisoning. Of these, 8 recovered, and 1 died of myelogenous leukemia. The authors present evidence that the abnormal rate of destruction of blood may be one of the factors in the production of anemia in cases of benzene poisoning. Hunter [200] emphasizes the importance of evaluation of the entire blood picture in the early diagnosis of benzene poisoning. Polycythemia, anemia, leukocytosis or leukopenia, leukemia or a leukemoid picture (myelogenous or lymphatic), eosinophilia, megalocytosis, microcytosis or immature elements in otherwise normal blood may characterize individual patients.

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196. Holmes, H. N.; Campbell, K., and Amberg, E. J.: The Effect of Vitamin C on Lead Poisoning, J. Lab. & Clin. Med. **24**:1119, 1939.

197. Tompsett, S. L., and Anderson, A. B.: Lead Poisoning: Lead Content of the Blood and of Excreta, Lancet **1**:559, 1939.

198. Lourau, M.; de Sacy, G. S., and Arthus, A.: Regénérations sanguines produites dans le saturnisme expérimental par un facteur hépotique hydrosoluble. Généralité de la réaction, Compt. rend. Soc. de biol. **130**:642, 1939.

199. Erf, L. A., and Rhoads, C. P.: The Hematological Effects of Benzene (Benzol) Poisoning, J. Indust. Hyg. & Toxicol. **21**:421, 1939.

200. Hunter, F. T.: Chronic Exposure to Benzene (Benzol): II. The Clinical Effects, J. Indust. Hyg. & Toxicol. **21**:331, 1939.

Mallory, Gall and Brickley [201] note that in cases of chronic benzene poisoning the entire hemopoietic system is affected. The bone marrow may be hypoplastic but is more frequently hyperplastic. Extramedullary hemopoiesis is noted in some persons. Hyperplasia is noted only after long exposure, whereas hypoplasia may appear with either short or long exposure. Curiously, hyperplasia is noted more commonly in males, whereas hypoplasia is more common in females. Some of the extramedullary changes resemble neoplasms. Two cases of leukemia were observed, in 1 of which there was frankly neoplastic tumor formation.

Feller [202] found that in rats the changes in the number of leukocytes in the peripheral blood and in the histologic structure of the tissues brought about by exposure to radium or to benzene were similar. However, there were many differences (eosinophil behavior, initial lowering of the absolute number of neutrophils and smaller variations in the number of erythrocytes and the hemoglobin percentage for the benzene-treated rats) that suggested a different mechanism in the action of the two agents. Recovery was more rapid after the injury from exposure to benzene. In workers with the rotogravure process in New York, Greenburg, Mayers, Goldwater and Smith [203] found serious abnormalities in the blood from benzene poisoning in the absence of definite clinical symptoms. The authors conclude that a reduction in the number of red blood cells and an increase in their size constitute a more sensitive and earlier sign of benzene poisoning than does a low leukocyte count. There is an enormous difference in individual susceptibility.

Oestreicher [204] found that yellow bone marrow was without effect on experimental benzene leukopenia in the rat. Thrombopenia with prolongation of the coagulation time of the blood is an initial and serious symptom in persons exposed to benzene, according to Mignolet.[205] In the majority of the cases the anemia is of the aplastic, hyperchromic type. Eosinophilia is relative and not absolute. Granulocytopenia is definite evidence that the poisoning is present, but the patient may respond to

201. Mallory, T. B.; Gall, E. A., and Brickley, W. J.: Chronic Exposure to Benzene (Benzol): III. Pathologic Results, J. Indust. Hyg. & Toxicol. **21**: 355, 1939.

202. Feller, A.: Der Einfluss des Radiums und des Benzols auf das Blut und auf die blutbildenden Organe mit besonderer Berücksichtigung der Leukozyten, Strahlentherapie **60**:393, 1937.

203. Greenburg, L.; Mayers, M. R.; Goldwater, L., and Smith, A. R.: Benzene (Benzol) Poisoning in the Rotogravure Printing Industry in New York City, J. Indust. Hyg. & Toxicol. **21**:395, 1939.

204. Oestreicher, F.: The Influence of Yellow Bone Marrow Extract on Experimental Benzene Leucopenia, Acta brev. Neerland. **9**:260, 1939.

205. Mignolet, F.: Les mémopathies du benzol, Sang **13**:268, 1939.

infection with neutrophilic leukocytosis. Penati and Vigliani [206] found that patients with chronic benzene intoxication may show aplastic anemia with either aplastic or hyperplastic bone marrow and with occasional myeloid metaplasia in the liver and spleen as well as acute or chronic leukemia.

Wallbach [207] has summarized his previous publication on the action of benzene and thorium-x on the blood. Lamy, Kissel and Pierquin [208] describe 10 cases of industrial benzene poisoning. Anemia, purpura and neutropenia were present in different patients. In the cases of mild involvement there was an erythroblastic reaction while in the cases of severe involvement the patients were marked by myeloid aplasia with hyperplasia of the cells of the reticulo-endothelial system. The prognosis is uncertain, and relapse may follow reexposure. Examination of the blood and bone marrow gives data of value in judging the prognosis. Repeated blood transfusions are of therapeutic value. The authors advocate legislative measures to prevent industrial benzene poisoning.

Other Agents.—Additional light on the mechanism of action of the roentgen ray on bone marrow is shed by the work of Bertola, Ravetta and Zelaschi.[209] Roentgen therapy (210 to 630 r) was applied every other day to 4 normal persons and the same therapy (60 to 150 r) to 8 patients with myelogenous and lymphatic leukemia and to 2 patients with malignant lymphogranuloma. The bone marrow was then studied from material taken by sternal puncture. No changes were noted in the erythroblastic tissue after irradiation in the normal persons or in the patients. In the leukoblastic tissue there appeared to be increased maturation of the cells, with fewer mitotic figures and prophases and more telophases. In cases of malignant lymphogranuloma the changes were less marked. These changes followed irradiation of either the bones or the spleen.

Congo red does not exert a hemostatic action in normal persons, according to the experiments of Richardson.[210] On intravenous injec-

206. Penati, F., and Vigliani, E. C.: Sul problema delle mielopatie aplastiche e leucemiche da benzolo, Rassegna di med. appl. lavoro indust. **9**:345, 1938.

207. Wallbach, G.: Résumé de mes examens comparés concernant l'action du benzol et du thorium X sur les réactions leucocytaires, Sang **13**:719, 1939.

208. Lamy, M.; Kissel, P., and Pierquin, L.: La myélotoxicose benzolique. Etude clinique et hématologique de dix cas d'intoxication professionelle par le benzol, Sang **13**:467, 1939.

209. Bertola, A.; Ravetta, M., and Zelaschi, C.: Roentgen-irradiazione dei tessuti emopoietici in soggetti normali ed emopatici (modificazioni del midollo osseo): Nota preventiva, Gazz. d. osp. **59**:1255, 1938.

210. Richardson, A. P.: Congo Red: Hematologic Actions, Am. J. M. Sc. **198**: 87, 1939.

tion of large doses there is a slight temporary anemia with hemagglutination, an effect absent with small doses. Moderate leukocytosis (neutrophilia) and a marked increase in the sedimentation rate result. Congo red in dilutions of 1:1,000 protects the erythrocytes of man against hemolysis from hypotonic solution of sodium chloride, hypertonic urea and sodium taurocholate in saline solutions and saponin in dextrose and saline solutions.

Experimental chronic cadmium poisoning in albino rats was found to produce anemia at all levels of dosage in the work of Wilson and De Eds.[211] The severity of the anemia (type not stated) increased with the percentage of cadmium added to the diet.

Meulengracht and Lundsteen[212] found that the gray–bluish violet cyanosis of acetanilid poisoning is due to a paramidophenol derivative and not to methemoglobin. The anemia may be very severe, with a hyperplastic bone marrow involving all of the cellular elements. Recovery is rapid, following discontinuance of ingestion of the poison.

BLOOD IN NEPHRITIS

Bock and Weyand[213] found that the anemia associated with various types of nephropathy is the result of increased destruction (indicated by urobilin determinations) and deficient rate of formation of the red blood cells. The lack of reticulocytosis is attributed to rapid aging of the red blood cells or to retarded elimination from the bone marrow. Nephropathies are divided into "pale hypertension" (nephroangiosclerosis with a blood pressure of 213 systolic and 129 diastolic), and "red hypertension" (nephroangiosclerosis with a blood pressure of 180 systolic and 90 diastolic). In the former condition the total mass of red blood cells is reduced and the plasma volume is increased, but in the latter the cell and plasma volume are normal. In cases of "pale hypertension" the red blood cells are thin and pale and are small in volume but normal in diameter as compared with normal erythrocytes in cases of "red hypertension." The most important factor of increase in cell catabolism, Bock and Weyand conclude, is not impairment of erythrocytes in the presence of contracted vessels but retention of urinary waste products.

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211. Wilson, R. M., and De Eds, F.: Experimental Chronic Cadmium Poisoning, Science **90**:498, 1939.

212. Meulengracht, E., and Lundsteen, E.: Die Cyanose und Anämie bei chronischer Acetanilid-Vergiftung, Folia haemat. **63**:89, 1939.

213. Bock, H. E., and Weyand, L.: Ueber Anämie bei Nierenkrankheiten; die Blutmauserung bei Kranken mit blassem Hochdruck und solchen mit Uebergangsformen vom roten zum blassen Hochdruck, Deutsches Arch. f. klin. Med. **184**:369, 1939.

Nolli [214] finds from sternal puncture of patients with nephritis that lesions of the bone marrow develop early. In the presence of renal sclerosis with anemia there is hypoplasia of the bone marrow. In the presence of acute diffuse hemorrhagic glomerulitis with anemia the marrow is of the type associated with posthemorrhagic anemia. In the presence of chronic renal inflammation the output of stem cells is diminished. Arsenic, iron and liver extract are said to be of value early in the disease. Terminally, there is a gelatinous transformation of the marrow.

Loeper and Perreau [215] found anemia to be present in 12 to 15 per cent of cases of chronic nephritis. It is usually orthochromic, occasionally hypochromic and rarely hyperchromic. Leukocytosis appears in about half of the cases, occasionally with eosinophilia. Possible mechanisms for the anemia are dilution of the blood, food deficiency, hemolysis, toxic action of amines and inhibition of blood regeneration. Therapeutic measures include small blood transfusions, liver therapy, administration of extract of kidney, institution of a diet rich in vitamins and administration of tryptophan, pancreatic extracts and charcoal to reduce intestinal putrefaction.

Kobryner and Rozenkranc [216] consider that the elevation in the number of neutrophils in conditions accompanied with edema is associated with the increased density of the blood (concentration effect). There is a reduction in number of these cells with diuresis. Nephritis caused little or no change in hemoglobin production in cases of induced hemorrhagic anemia in the early stages of the disease in a group of dogs studied by Whipple and Robscheit-Robbins.[157] In the late stages of nephritis there was no change or moderate change in hemoglobin regeneration as compared with that observed in "standard anemic dogs." The average production of hemoglobin was 70 per cent of the normal.

Ultrafiltrates of serum from patients with uremia, with renal insufficiency and with various other diseases associated with changes in blood chemistry were injected into rabbits by Marcolongo and Leone.[217] Alterations of the hemopoietic organs, especially hemosiderosis of the spleen, parenchymal degenerations, leukocytic changes and specific alterations due to the anemia-producing properties of the uremic blood serum were noted. This "ultrafiltrate anemia" had no specific character-

214. Nolli, B.: L'esplorazione funzionale del midollo osseo nelle nefriti, Gior. di clin. med. **20**:1023, 1939.

215. Loeper, M., and Perreau, P.: L'anémie brightique, Sang **13**:113, 1939.

216. Kobryner, A., and Rozenkranc, D.: Sur la pseudo-leucocytose dans les états œdémateux, Sang **13**:870, 1939.

217. Marcolongo, F., and Leone, P.: Tentativi di riproduzione sperimentale di anemie con ultrafiltrato di siero uremici, Haematologica **20**:49, 1939.

istics. In some animals the volume and the diameter of the red blood cells were diminished, while in others both were increased. The bone marrow picture was always that of "secondary" anemia.

POLYCYTHEMIA

Émile-Weil, Isch-Wall, Perlès and Aschkenazy [218] present a comparative study of the material aspirated by sternal, splenic and hepatic punctures in a case of polycythaemia vera. The greatest pathologic variation was noted in the marrow (hyperplasia of the erythropoietic tissue).

Reznikoff [219] summarizes the recent concepts of polycythemia, showing the thickening of the arterioles and capillary walls in the bone marrow and illustrating the use of acetylphenylhydrazine, venesection and roentgen rays by the spray technic in treating 3 patients.

Various types of erythroblastic anemia have been described. In Israël's [220] case a 42 year old woman had an illness of several months' duration, characterized by splenomegaly, hepatomegaly, severe anemia, enormous numbers of normoblasts and megaloblasts in the blood and hyperplasia of these elements in the bone marrow. Roentgen irradiation, liver, iron, arsenic and transfusions failed to prevent a fatal termination. Israël eliminated leukoerythroblastic anemia, erythroblastic disease of adults, polycythaemia vera and a leukemoid condition and called the disease true erythremia, analogous to leukemia.

While true polycythemia is rare in children, polycythemia in various types may appear. Kellman's [221] patient, a 6 year old girl, showed a temporary rise in the red blood cell count to 9,000,000 per cubic millimeter, with 77,500 leukocytes, of which 82 per cent were lymphocytes. A spontaneous remission of three years' duration was in progress when the case was described.

Schippers [222] studied 6 cases of polycythemia in infants ranging from a few days to 5 weeks of age. Cerebral and cardiac anomalies were not the cause, as the polyglobulism disappeared after administration of oxygen. There was no normoblastosis and no hemolytic icterus, suggesting retarded hemolysis. Occasional symptoms were tumor of the

218. Émile-Weil, P.; Isch-Wall, P.; Perlès, S., and Aschkenazy: Les ponctions couplées dans la polyglobulie simple (type Vaquez), Sang **13**:96, 1939.

219. Reznikoff, P.: Polycythemia, Bull. New York Acad. Med. **15**:311, 1939: Polycythemia, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p. 207.

220. Israëls, M. C. G.: Immature Cell Erythraemia in an Adult, J. Path. & Bact. **47**:299, 1939.

221. Kellman, L.: Primary Polycythemia with Leukemic Manifestations, Am. J. Dis. Child. **58**:146 (July) 1939.

222. Schippers, J. C.: Polyglobulie prolongée après la naissance. Rev. franç. de pédiat. **15**:102, 1939.

arm, hypertonia and somnolence, but some patients were asymptomatic. There was no recurrence of the disease.

Reifenstein [223] describes a case of erythremia with gout evolving into aleukemic myelogenous leukemia with anemia. The bone marrow was hyperplastic and was regarded as typical of myelogenous leukemia.

Familial polycythemia was studied by Nadler and Cohn [224] in the cases of 4 patients aged 11, 13, 16 and 18 years respectively. There was no leukocytosis, no increase in the basal metabolic rate and no evident splenomegaly, but the circulating cell mass was greatly increased, as in cases of polycythaemia vera.

Coronary thrombosis may be a complication of polycythaemia vera, as is illustrated by the cases reported by Miller.[225] Of 7 patients examined at autopsy, 3 had myocardial alterations with associated coronary occlusions, and 2 showed extensive similar changes in the heart muscle but no thrombus in the coronary tributaries, while 2 showed no myocardial damage or myocardial thrombosis. The similarity of precordial pain in polycythemia and anemia is noted.

Thrombophlebitis of the hepatic veins secondary to polycythaemia vera was noted in Altschule and White's [226] patient.

In cases of polycythemia, Émile-Weil, Aschkenazy and Capron [227] found that the elevated glutathione content is associated with the degree of polyglobulism, with wide variations in the oxidized form. The value for total glutathione in cases of polycythemia varied from 49.4 to 91.1 mg. per hundred cubic centimeters; that for reduced glutathione, from 44.7 to 91.0 mg., and that for oxidized glutathione, from 0 to 9.3 mg.

Vogelensang [228] found very high values for zinc in the blood of a patient with polycythemia.

Davis [229] found that the polycythemia produced in dogs by exposure to low atmospheric pressures, as well as that caused by exercise or cobalt

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223. Reifenstein, G. M.: A Case of Erythremia, Gout and Subleukemic Myelosis, Am. J. M. Sc. **197**:215 (Feb.) 1939.

224. Nadler, S. B., and Cohn, I.: Familial Polycythemia, Am. J. M. Sc. **198**: 41, 1939.

225. Miller, H. R.: The Occurrence of Coronary Artery Thrombosis in Polycythemia Vera, Am. J. M. Sc. **198**:323, 1939.

226. Altschule, M. D., and White, G.: Chiari's Syndrome in Patient with Polycythemia Vera: Report of Case, New England J. Med. **220**:1030, 1939.

227. Émile-Weil, P.; Aschkenazy, A., and Capron, L.: Le glutathion sanguin dans les polyglobulies, les leucémies et les érythroblastoses chroniques, Sang **13**: 705, 1939.

228. Vogelensang, E. H.: Occurrence of Zinc in Human Blood, Pharm. Weekbl. **76**:89, 1939.

229. Davis, J. E.: Depression of Polycythemia by Choline Hydrochloride, Proc. Soc. Exper. Biol. & Med. **40**:445, 1939; Depression of Experimental Polycythemias by Choline Hydrochloride or Liver Administration, Am. J. Physiol. **127**:322, 1939.

chloride, could be reduced and the blood restored to the normal level by oral administration of 8 mg. of choline hydrochloride per kilogram of body weight per day. A similar effect could be produced by the feeding of raw hog or beef liver in amounts of 75 Gm. per day. Choline chloride did not affect the erythrocyte count of normal dogs. The author concludes that the choline content of raw liver is the effective agent and suggests that it may be of value in the treatment of polycythaemia vera.

In normal unanesthetized dogs, Palitz [230] found that artificial fever of an hour's duration caused an increase in erythrocyte count, hematocrit volume and concentration of serum protein. This reaction was absent after the spleen was removed.

While the blood volume may be 60 to 70 per cent below normal in cases of anemia due to chronic loss of blood, nephritis or hemolysis or in cases of "idiopathic" hypochromic anemias, Gibson, Harris and Swigert [231] found that there is a great increase in the total blood volume in cases of polycythaemia vera. This is due to the increase in cell volume, the plasma volume remaining normal. Repeated phlebotomies reduced the cell volume and hence the total volume, as the plasma volume remained unchanged.

Polycythemia was produced in rats by the feeding of fresh or acetone-extracted pituitary glands by Flaks, Himmel and Zotnik.[232] A similar polyglobulism was noted in some hypophysectomized animals as well as in those treated with a protein-free extract of pituitary free from gonadotropic, growth and thyrotropic hormones. Reticulocytosis developed during the injection. The authors favor the theory of a hemopoietic hormone.

Polonovski and Briskas [233] feel that in rats and dogs cobalt polycythemia is probably the result of an increase in the total blood volume resulting from the toxic action of cobalt, rather than the new formation of red blood cells.

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230. Palitz, L. L.: Splenic Volume and the Polycythemia of Artificial Fever in Intact, Unanesthetized Dogs, Am. J. Physiol. **125**:607, 1939

231. Gibson, J. G., Jr.; Harris, A. W., and Swigert, V. W.: Clinical Studies of the Blood Volume: VIII. The Blood Volume in Secondary Anemia and Polycythemia Vera, J. Clin Investigation **18**:621, 1939.

232. Flaks, J.; Himmel, I., and Zotnik, A.: La polyglobulie provoquée par les extraits de lobe antériem d'hypophyse prouve l'existence d'une hormone hémopoiétique, Presse méd. **46**:1506, 1938.

233. Polonovski, M., and Briskas, S.: Contribution a l'étude de l'action hémopoiétique du cobalt au cours de l'anime provoquée chez le jeune rat carencé, Compt. rend. Soc. de biol. **130**:1588, 1939; Le rôlé des sels de cobalt dans l'anémie provoquée chez le chien, ibid. **130**:1590, 1939.

Kleinberg, Gordon and Charipper,[234] however, found that cobalt salts injected into rabbits subjected to repeated bleedings or treated with benzene promote rapid recovery from anemia by stimulation of the formation of erythrogenic precursors in the bone marrow.

Okrainetz [235] has described in detail the treatment of polycythemia by "total body irradiation." A symptomatic remission of fifteen months' duration was produced by giving 235 r (measured in air) to the anterior surface of the body and 210 r posteriorly, in individual doses of 25 r over a period of thirty-five days. With the subsequent relapse, the symptoms and the polyglobulia returned, but four treatments (25 r each) were sufficient to produce a remission for another year. The author feels that small doses given by total body irradiation, with protection of the eyes, spleen and, in this case, ovaries, is preferable to larger doses over single bones.

Anderson, Geill and Samuelsen [236] treated 2 patients with polycythemia by roentgen therapy over the pylorus. The position was located fluoroscopically. Four series of treatments were given at monthly intervals. Hematologic improvement was noted. Hitzenberger in 1931 used a similar type of therapy, with production of a temporary remission. The underlying theory was based on the hope of destroying or inhibiting the production of the intrinsic factor of Castle, thus delaying production of red blood cells.

Kaplan [237] finds that polycythaemia vera is most satisfactorily controlled by high voltage roentgen therapy over the sternum and ribs. He recommends 200 kilovolts potential with filtration of 0.5 mm. of copper plus 1 mm. of aluminum at a distance of 40 to 50 cm. Individual doses of 150 to 200 r (measured in air) are repeated every third day. Remissions lasting as long as forty weeks have been produced. When intensive irradiation is directed to the spleen, there is a rise in the red blood cell count.

The treatment of polycythemia associated with pulmonary hypertension (Ayerza's disease), complicated by arterial hypertension and marked obesity, should aim to reduce the viscosity of the blood and prevent thrombosis, according to the experience of Olsen and Willius.[238]

234. Kleinberg, W.; Gordon, A. S., and Charipper, M. A.: Effect of Cobalt on Erythropoiesis in Anemic Rabbits, Proc. Soc. Exper. Biol. & Med. **42**:119, 1939.

235. Okrainetz, C. L.: Total Body Irradiation in Polycythemia Vera, M. Woman's J. **46**:203, 1939.

236. Anderson, F.; Geill, T., and Samuelsen, E.: Polycythemia Treated with Roentgen Irradiation of Pylorus Organ, Acta med. Scandinav. **97**:547, 1938.

237. Kaplan, I.: Treatment of Polycythemia with Roentgen Ray, Radiology **33**:166-169, 1939.

238. Olsen, A. M., and Willius, F. A.: Cardiac Clinics: LVI. Clinic on Cardiac Failure Resulting from Pulmonary Hypertension (Ayerza's Disease) Complicated by Arterial Hypertension and Marked Obesity, Proc. Staff Meet., Mayo Clin. **14**:89, 1939.

Venesection is the method of choice. Some degree of activity should be allowed to the patient, and unnecessary injury of the veins is to be avoided to prevent local thrombosis.

The treatment advocated by Herzog and Kleiner [239] consists in limiting the animal protein to 0.7 Gm. a day. There was a definite decrease in the number of red blood cells, in some cases at the end of one week and in others at longer intervals. Hypertension was lowered and splenomegaly decreased. Of 19 cases, the treatment was successful in 17. A less strict diet (1 pint of milk, 100 Gm. of cheese, 200 Gm. of fish daily; 3 eggs or 150 Gm. of veal twice weekly) was prescribed when the improvement in the blood set in.

PURPURA

Of the many bleeding disorders, purpura haemorrhagica is one of the least understood. This is undoubtedly due to the multiple etiologic factors and to the confusion created by the various classifications. Forkner,[240] in an excellent review of the hemorrhagic diseases, states that they should be classified according to their clinical picture rather than according to the pathologic condition present or the physiologic mechanisms involved. In spite of this viewpoint, he includes the latter in his excellent tables. Six cases of essential thrombopenic purpura have been studied by Heinild.[241] According to this investigator, the outstanding characteristics of the disease are the unknown cause, the spontaneous hemorrhages, the decrease or absence of platelets, the prolonged bleeding time and the poor clot retraction. The course may be acute or chronic, and the disease usually occurs in women. In addition to the essential type of thrombopenic purpura, the author also described symptomatic, allergic and hypersplenic purpura.

Elliott [242] classifies purpuras as primary or secondary. The latter may have such etiologic factors as infections, poisons, nutritional deficiencies and disturbances of the reticuloendothelial system and bone marrow. The platelets may or may not be reduced in number. The cause of the primary type of purpura is not known. Elliott, in addition

239. Herzog, F., and Kleiner, G.: Ergebnis der Diätbehandlung in neunzehn Fällen von Polyzythämie, Deutsche med. Wchnschr. **65**:719, 1939; Therapy of Polycythemia: Results in Nineteen Cases, Orvosi hetil. **83**:357, 1939.

240. Forkner, C. E.: An Attempt to Consolidate and to Clarify Present Views Concerning the Anemias and the Hemorrhagic Disorders, Proc. A. Life Insur. M. Dir. America (1938) **25**:258, 1939.

241. Heinild, S.: Observations on Essential Thrombopenia (Morbus Maculosus Werlhofii), Acta med. Scandinav. **98**:385, 1939.

242. Elliott, R. H. E.: Diagnostic and Therapeutic Considerations in the Management of Idiopathic Thrombocytopenic Purpura, Bull. New York Acad. Med. **15**:197, 1939.

to the characteristics of the disorder mentioned by the previous writers, states that the course in adults and children varies. With the younger patients spontaneous recoveries are common. This opinion is shared by Rosenthal,[243] who has adequately reviewed the etiology, course and treatment of the disease.

So-called secondary purpura due to various drugs has been reported by many authors. McGovern and Wright[244] and Huber[245] describe cases in which the offending substance was sedormid. Sexton[246] and Wyatt[247] noted the occurrence of bleeding following the use of arsphenamine.

The role of the spleen in the production of thrombopenic purpura was investigated by Major and Weber[248] and by Pohle and Meyer.[249] These authors attempted to reproduce the disease in rabbits by injecting extracts prepared from spleens removed from patients with thrombopenic purpura. All attempts met with failure. Major and Weber state that their failure to substantiate the previous reports that a platelet-reducing substance is present may be due to differences in their extracts. Pohle and Meyer offer no explanation for their failure to reproduce the disease but state definitely that a platelet-reducing substance does not exist in the spleens of patients with essential purpura.

The pathologic anatomy of experimental thrombopenic purpura in the dog was studied by Toncantins and Stewart.[250] Antiplatelet serum was prepared from washed platelets of dogs and injected into rabbits. The experiments included several groups or types: (1) fatal, (2) serial short intravenous, (3) multiple doses and (4) control. In all instances generalized hemorrhages were produced. The purpura produced by the intraperitoneal route, according to the authors, simulated true purpura as seen in man. The course was described as follows: in the acute stage

243. Rosenthal, N.: The Course and Treatment of Thrombopenic Purpura, J. A. M. A. **112**:101 (Jan. 14) 1939.

244. McGovern, T., and Wright, I.: Purpura Haemorrhagica Following Use of Sedormid, J. A. M. A. **112**:1687 (April 29) 1939.

245. Huber, H. H.: A Case of Purpura Haemorrhagica Resulting from Sedormid, J. A. M. A. **113**:674 (Aug. 19) 1939.

246. Sexton, G. B.: Caution in Arsphenamine Therapy, Canad. M. A. J. **40**:378, 1939.

247. Wyatt, W.: A Case of Peripheral Neuritis Due to Neoarsphenamine, and Purpura Hemorrhagica Due to Bismuth Arsphenamine Sulphonate, M. Rec. **149**:349, 1939.

248. Major, R. H., and Weber, C. J.: Is There a Platelet Reducing Substance in the Spleen of Thrombocytopenic Purpura? J. Lab. & Clin. Med. **25**:10, 1939.

249. Pohle, F. J., and Meyer, O. O.: Inability to Demonstrate a Platelet Reducing Substance in an Acetone Extract of the Spleen from Patients with Idiopathic Thrombocytopenic Purpura, J. Clin. Investigation **18**:537, 1939.

250. Toncantins, L. M., and Stewart, H. L.: Pathological Anatomy of Experimental Thrombopenic Purpura in the Dog, Am. J. Path. **15**:1, 1939.

(first to fifth day), thrombopenia, a prolonged bleeding time, hemorrhage, edema, and deposition of pigment were the outstanding characteristics; the intermediate stage (fifth to tenth day) was identified by the occurrence of multiple vascular thrombi, principally in the spleen, and a short bleeding time, and the third, or reactive, stage appeared after the tenth day. The platelet count was normal or increased, follicular hemorrhages were present in the spleen and hyperplastic changes were noted in the bone marrow, the spleen, the lymph nodes, the thymus and Peyer's patches. In summary, these investigators point out that hemorrhages are seen usually in organs with changing pressures and are rare in more stable organs. Trauma must also be considered as an important factor.

Multiple cases of atypical purpura have been reported. Schindler [251] describes chronic localized gastric purpura and believes that it is a new disease. He also stresses its relation to chronic gastroduodenal ulcer and suggests the possibility that it may be the initial lesion in the development of the ulcer. Leukothrombopenia associated with increased capillary permeability is described by Madison and Squier.[252] These authors are of the opinion that this is a definite clinical syndrome. The characteristics of renal purpura and its differences from the renal hemorrhages associated with thrombopenic purpura are reported by Dukes.[253] Levinson [254] reviews the history of the Waterhouse-Friderichsen syndrome and reports a case studied by himself. The disease is characterized by the sudden onset of malaise, vomiting, diarrhea, fever, rapid pulse, cyanosis, purpura, lethargy, coma and death. The cause is not definitely known, though bacteremia or toxemia is considered the most likely. Pathologic studies reveal hemorrhages in the adrenal glands in addition to generalized purpura.

The treatment of purpura is dependent on the cause, which must be established. It must also be kept in mind that relapses and remissions are common and that the therapeutic results obtained may be dependent to a certain extent on this characteristic of the disease. As is suggested by Limarzi and Schleicher,[255] studies of the bone marrow are of considerable aid in identifying true thrombopenic purpura and in determining when splenectomy is indicated. Heinild is of the opinion that

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251. Schindler, R.: Chronic Localized Gastric Purpura, Am. J. Digest. Dis. **5**:796, 1939.

252. Madison, F. W., and Squier, T. L.: Leukothrombopenia with Increased Capillary Permeability, J. A. M. A. **112**:879 (March 4) 1939.

253. Dukes, C. E.: Renal Purpura, Proc. Roy. Soc. Med. **32**:1322, 1939.

254. Levinson, S. A.: The Waterhouse-Friderichsen Syndrome, J. Pediat. **14**: 506, 1939.

255. Limarzi, L. R., and Schleicher, E. M.: Bone Marrow in the Active Phase of Essential Thrombopenic Purpura, J. A. M. A. **112**:899 (March 4) 1939.

splenectomy is of considerable value for purpura but recommends a trial of conservative therapy first. Elliott compared the results following splenectomy in cases of true thrombopenia and in cases of atypical purpura. In the first group, of 21 cases, 13 patients were cured, 5 were definitely improved, 2 were improved but not free from symptoms, and 1 died. In the second group, of 11 cases, there were 4 cures and 5 deaths, and 2 patients showed no improvement.

Bernstein and his co-workers [256] report the unusual occurrence of idiopathic thrombopenia in pregnancy and the neonatal period. Splenectomy was successfully performed during the sixth month of pregnancy. Menorrhagia as the outstanding feature of purpura is noted by Jennings and Castleden [257] and by Israel and Mendell.[258] Splenectomy was of little benefit to the patient of Jennings and Castleden but produced a cure in the patient of Israel and Mendell. Vaughan and Wright [259] observed 6 patients for at least ten years after splenectomy. They concluded that the results of this type of therapy in properly selected cases are not only good but permanent.

This opinion is shared by Rosenthal,[243] who, in addition, has summarized the results obtained with various other types of therapy. Ascorbic acid, liver extract, parathyroid extract and roentgen irradiation are of no value. Sesame oil is useless, a conclusion substantiated by Olson.[260] Snake venom is recommended for secondary purpura. Transfusions are of temporary help. Ligation of the splenic artery fails to give any relief.

HEMOPHILIA

As with many other diseases, the cause of hemophilia has not been identified. Howell [261] states that there is a deficiency in the plasma of some substance as yet unknown. For brevity he uses the term "thromboplastin" and distinguishes two types, plasma thromboplastin and tissue thromboplastin. Plasma thromboplastin can be obtained from citrated blood by saturation with carbon dioxide or by addition of acid. This

256. Bernstein, P.; Newman, A. B., and Hitzig, W. M.: The Problem of Idiopathic Purpura Hemorrhagica in Pregnancy and the Neonatal Period, Am. J. Obst. & Gynec. **38**:323, 1939.

257. Jennings, G. H., and Castleden, L. I. M.: Thrombocytopenic Purpura, Lancet **1**:931, 1939.

258. Israel, S. L., and Mendell, T. H.: Severe Menorrhagia as the Only Symptom of Essential Thrombocytopenic Purpura Cured by Splenectomy, Am. J. Obst. & Gynec. **38**:339, 1939.

259. Vaughan, S. L., and Wright, T.: Purpura Haemorrhagica, with Special Reference to Permanence of Remission Following Splenectomy, J. A. M. A. **112**: 2120 (May 27) 1939.

260. Olson, K. B.: The Effect of Sesame Oil ("T-Factor") on the Platelet Count, Proc. Soc. Exper. Biol. & Med. **41**:643, 1939.

261. Howell, W. H.: Hemophilia, Bull. New York Acad. Med. **15**:3, 1939.

substance is associated with all proteins in the blood. In hemophilic blood it is present in smaller amounts than normal. This fact was established by adding thromboplastin extracts from normal and hemophilic blood to hemophilic blood and observing the differences in clotting time. Similar results were noted with tissue thromboplastin. In the author's opinion, platelets are the source of plasma thromboplastin; if the plasma is normal hemophilic platelets will react normally, but otherwise they appear to be more stable, with a resulting prolongation of the clotting time.

The coagulation defect associated with hemophilia has also been investigated by Lozner and his co-workers.[262] These investigators prepared a clot-promoting substance from normal human plasma free from fibrinogen and prothrombin. When this material was added to hemophilic blood, clotting proceeded at a rate proportional to the amount of substance added. When the clot-promoting substance was injected intravenously, the coagulation time readily decreased. Multiple injections at six hour intervals further decreased the clotting time; there was no evidence of any refractory period.

Ferguson [263] has also studied the mechanism of clotting in hemophiliacs. He believes that there is a deficiency in the amount of "thromboplastic enzyme" in hemophilic blood and that because of the lack of this substance there is a delay in coagulation. Bendien and van Creveld [264] prepared a globulin-like protein substance and investigated its coagulation-promoting activity, especially in relation to hemophilia. This substance was ineffective when administered orally or intramuscularly but readily decreased the clotting time when injected intravenously. Similar results were obtained with a preparation from placenta, though to a lesser degree. It is the author's opinion that this coagulation-promoting substance is related to prothrombin.

Platelet studies of normal men, of women (menstruating and nonmenstruating) and of persons with bleeding disorders were made by Lee and Erickson.[265] From their observations they conclude that

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262. Lozner, E. L.; Kark, R., and Taylor, F. H. L.: The Coagulation Defect in Hemophilia: The Clot Promoting Activity in Hemophilia of Berkefelded Normal Human Plasma Free from Fibrinogen and Prothrombin, J. Clin. Investigation **18**:603, 1939.

263. Ferguson, J. H.: The Clotting of Hemophilic Plasma by Thromboplastic Enzyme, Am. J. Physiol. **126**:669, 1939.

264. Bendien, W. M., and van Creveld, S.: On Some Factors of Blood Coagulation, Especially with Regard to the Problem of Hemophilia, Acta med. Scandinav. **99**:12, 1939.

265. Lee, P., and Erickson, B. N.: Platelet Studies in Normal Men and Women (Menstruating and Nonmenstruating) and Subjects with Bleeding Disorders, J. Lab. & Clin. Med. **24**:821, 1939.

there is a similarity in the abnormal clotting of the blood of menstruating women and that of hemophiliacs.

Owing to the bleeding tendency, complications often arise in cases of hemophilia. Paltrinieri [266] and Newcomer [267] emphasize the frequency of hemorrhage into joints with contractures. The dangers to be encountered in hemophilia when operations are necessary are stressed by Vance.[268] His conclusions are most important. Hemophiliacs should not be subjected to an operation unless the danger to life is increased as the result of deprivation of the operation. If surgical intervention is contemplated, the patient should be adequately prepared with transfusions. Howell [261] also states that the only reliable treatment for hemophilia is transfusion.

BLOOD CLOTTING

A most complete résumé on vitamin K has been published by Snell and Butt.[269] These authors point out the difficulties associated with the problem related to the defining of a unit of the vitamin. Ansbacher [270] defines a unit of vitamin K as the minimum amount necessary to render the clotting time of the blood of the vitamin K–deficient chick weighing 70 to 100 Gm. normal within six hours after administration. This unit equals 20 Dam units. Thayer and his co-workers [271] assayed vitamins K_1 and K_2 and defined a unit as that quantity of vitamin K which produces a clotting time of ten minutes or less in 50 per cent of a group of 10 or more chicks which have been fed for the fourteen days immediately following receipt from the hatcher on a diet practically devoid of vitamin K. By these standards, vitamin K_1 contains approximately 1,000 units per milligram and vitamin K_2 about 600 units per milligram. Dam and Glavind and Almquist and his associates have also established units of activity which are at considerable variance with the units just defined. It is readily apparent that for the present no unit can arbitrarily be established which would be suitable to all investigators.

The isolation and purification of vitamin K may soon be a reality. Almquist and Klose [272] have prepared a choleic acid derivative, which

266. Paltrinieri, M.: Osservazioni di retrazione ischemiche di Volkmann in emofilici, Bull. d. sc. med., Bologna **111**:203, 1939.

267. Newcomer, N. B.: The Joint Changes in Hemophilia, Radiology **32**: 573, 139.

268. Vance, C. A.: Surgery in Hemophilia, Ann. Surg. **109**:872, 1939.

269. Snell, A. M., and Butt, H. R.: Supplementary Report on Vitamin K, J. A. M. A. **113**:2056 (Dec. 2) 1939.

270. Ansbacher, S.: A Quantitative Biological Assay of Vitamin K, J. Nutrition **17**:303, 1939.

271. Thayer, S. A.; McKee, R. W.; Binkley, S. B.; MacCorquodale, D. W., and Doisy, E. A.: Assay of Vitamin K Concentrates, Proc. Soc. Exper. Biol. & Med. **40**:478, 1939; The Assay of Vitamins K_1 and K_2, ibid. **41**:194, 1939.

272. Almquist, H. J., and Klose, A. A.: The Isolation of Vitamin K as a Choleic Acid, J. Am. Chem. Soc. **61**:745, 1939.

is a yellow crystalline substance with a melting point of 186 C. The K vitamin can be separated from this substance as a viscous, slightly pigmented oil. The effect of this substance on prothrombin levels when fed orally to rats with bile fistulas was investigated by Cohn and Schmidt.[273] Although their results were poor, it is their opinion that the doses of the material were too small. By a process of molecular distillation and chromatographic methods, Dam and his co-workers [274] prepared a substance which they believed was the pure vitamin K. It contains about 20,000,000 Dam units per gram by biologic assay. Chemically, it appears as a clear yellowish oil containing carbon, hydrogen and oxygen and is free of nitrogen.

McKee and his collaborators [275] isolated vitamins K_1 and K_2 from alfalfa and putrefied fish meal respectively. Subsequent work [276] suggested that the vitamins have a quinoid structure. Almquist and Klose [276] noted that phthiocol has physical and chemical properties similar to pure vitamin K. Fernholz and Ansbacher [277] demonstrated that synthetic phthiocol has antihemorrhagic properties and noted its powerful curative effects in chicks deficient in vitamin K. Phthiocol was first isolated (1933) and synthesized (1934) by Anderson and his co-workers. The antihemorrhagic activity of phthiocol is considered by Almquist and Klose [278] to be somewhere between that of methylnaphthoquinone and hydroxynaphthoquinone. The latter group appears to reduce the activity, while the former is functionally important. Ansbacher and Fernholz [279] agree with the opinion of Almquist and Klose that phthiocol is of less potency than is the more complex form of vitamin K in alfalfa.

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273. Cohn, E. J., and Schmidt, C. L. A.: Effect of Choleic Acid of Vitamin K on Prothrombin Levels of Bile Fistula Rats, Proc. Soc. Exper. Biol. & Med. **41**:443, 1939.

274. Dam, H.; Geiger, A.; Glavind, J.; Karrer, P.; Karrer, W.; Rothschild, E., and Solomon, H.: Isolierung des Vitamins K in hochgereinigter Form, Helvet. chim. acta **22**:310, 1939.

275. McKee, R. W.; Binkley, S. B.; MacCorquodale, D. W.; Thayer, S. A., and Doisy, E. A.: The Isolation of Vitamins K_1 and K_2, J. Am. Chem. Soc. **61**: 1295, 1939. Binkley, S. B.; MacCorquodale, D. W.; Cheney, L. C.; Thayer, S. A.; McKee, R. W., and Doisy, E. A.: Derivatives of Vitamins K_1 and K_2, ibid. **61**: 1612, 1939.

276. Almquist, H. J., and Klose, A. A.: The Antihemorrhagic Activity of Pure Synthetic Phthiocol, J. Am. Chem. Soc. **61**:1611, 1939.

277. Fernholz, E., and Ansbacher, S.: Vitamin K Activity of Synthetic Phthiocol, Science **90**:215, 1939.

278. Almquist, H. J., and Klose, A. A.: The Antihemorrhagic Activity of Certain Naphthoquinones, J. Am. Chem. Soc. **61**:1923, 1939.

279. Ansbacher, S., and Fernholz, E.: Simple Compounds with Vitamin K Activity, J. Am. Chem. Soc. **61**:1924, 1939.

The structure of the antihemorrhagic vitamin has been the subject of considerable investigation. Thayer and his colleagues,[280] as well as MacCorquodale and his associates,[281] found that 2-methyl-1, 4-naphthoquinone is the most effective substance, but its activity compared to the natural vitamins K_1 and K_2 is negligible. The K_1 molecule is believed to be 2-ethyl-3-phytyl-1, 4-naphthoquinone. It is suggested by Fieser and his collaborators[282] that the structure of vitamin K_1 is 2, 6 (?) - dimenthyl-3-phytyl-1, 4-naphthoquinone and that the structure of vitamin K_2 is 2, 3-difornesyl-1, 4-naphthoquinone. By means of synthesis, Binkley and his associates[283] demonstrated conclusively that vitamin K_1 is 2-methyl-3-phytyl-1, 4-naphthoquinone. Fieser, Campbell, Fry and Gates[284] describe the synthesis of vitamin K_1 and confirm its chemical structure. Since this synthetic compound has an activity equivalent to that of pure vitamin K_1, it is suggested by Thayer and his co-workers[285] that it be adopted as a basic standard for the assay of vitamin K. With the exception of its instability when exposed to light,[286] it has all the necessary requisites of a product suitable for standardization.

The methods of determining prothrombin time present a problem which at present does not appear too important, since the nature of prothrombin is not known. Ziffren and his associates[287] describe a "bedside" technic for determining the clotting time of an unknown specimen of blood and comparing the results with those obtained with

280. Thayer, S. A.; Cheney, L. C.; Binkley, S. B.; MacCorquodale, D. W., and Doisy, E. A.: Vitamin K Activity of Some Quinones, J. Am. Chem. Soc. **61**: 1932, 1939.

281. MacCorquodale, D. W.; Binkley, S. B.; Thayer, S. A., and Doisy, E. A.: On the Constitution of Vitamin K_1, J. Am. Chem. Soc. **61**:1928, 1939.

282. Fieser, L. F.; Bowen, D. M.; Campbell, W. P.; Fieser, M.; Fry, E. M.; Jones, R. N.; Riegel, B.; Schweitzer, C. E., and Smith, P. G.: Quinones Having Vitamin K Activity, J. Am. Chem. Soc. **61**:1925, 1939.

283. Binkley, S. B.; MacCorquodale, D. W.; Thayer, S. A., and Doisy, E. A.: The Isolation of Vitamin K_1, J. Biol. Chem. **130**:219, 1939.

284. Fieser, L. F.; Campbell, W. P.; Fry, E. M., and Gates, M. D., Jr.: Synthetic Approach to Vitamin K_1, J. Am. Chem. Soc. **61**:2559, 1939.

285. Thayer, S. A.; Binkley, S. B.; MacCorquodale, D. W.; Doisy, E. A.; Emmett, A. D.; Brown, R. A., and Bird, O. D.: Vitamin K Potencies of Synthetic Compounds, J. Am. Chem. Soc. **61**:2563, 1939.

286. MacCorquodale, D. W.; Binkley, S. B.; McKee, R. W.; Thayer, S. A., and Doisy, E. A.: Inactivation of Vitamin K by Light, Proc. Soc. Exper. Biol. & Med. **40**:482, 1939.

287. Ziffren, S. E.; Owen, C. A.; Hoffman, G. R., and Smith, H. P.: Control of Vitamin K Therapy: Compensatory Mechanisms at Low Prothrombin Levels, Proc. Soc. Exper. Biol. & Med. **40**:595, 1939; Clinical and Experimental Studies on Vitamin K, J. A. M. A. **113**:380 (July 29) 1939.

normal blood. Thromboplastin is added to each specimen. The unknown is expressed in percentage of the normal. Pohle and Stewart [288] studied the Quick method for quantitative determination of prothrombin and criticized it on the basis that there are too many variables which influence the results. In answer to this criticism, Quick [289] pointed out that by standardizing the technic the variables can be discounted. In justification of the various tests recommended, it should be kept in mind that, whichever method is used for determining the prothrombin deficiency, the results are dependent on the experience of the physician concerned. Boyce and McFetridge [290] have devised a serum volume test for determination of the bleeding tendency in cases of jaundice. Three cubic centimeters of blood is removed from the patient and permitted to stand at room temperature for four hours. The serum volume divided by 1.5 cc. gives an index of 1 or more, which is considered normal. Indexes less than 1 are indicative of hemorrhage. This test proved to be satisfactory in 21 cases studied.

Several conditions in which prothrombin deficiency may exist and can be corrected by administration of vitamin K have been reported. Waddell and Guerry [291] noted that the prothrombin level in newborn infants is often low and that there is considerable variation in individual infants from day to day. The newborn with a bleeding tendency and those with low prothrombin levels readily responded to vitamin K therapy. Quick and Grossman [292] noted that the prothrombin concentration was high for the first six hours after birth, rapidly decreased for the next twenty-four to forty-eight hours and then gradually increased. They suggest that an important factor in the increase of prothrombin is synthesis of vitamin K by bacteria in the gastrointestinal tract. Owen and his co-workers [293] noted a continual decrease in the prothrombin

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288. Pohle, F. J., and Stewart, J. K.: A Study of the Quick Method for the Quantitative Determination of Prothrombin, with Suggested Modifications, Am. J M. Sc. **198**:622, 1939.

289. Quick, A. J.: Calcium Factor in Quantitative Determination of Prothrombin, Proc. Soc. Exper. Biol. & Med. **40**:206, 1939.

290. Boyce, F. F., and McFetridge, E. M.: The Serum Volume Test for the Hemorrhagic Diathesis in Jaundice: Further Observations, New Orleans M. & S. J. **91**:357, 1939.

291. Waddell, W. W., Jr., and Guerry, D., III: Effect of Vitamin K on the Clotting Time of the Prothrombin and the Blood, J. A. M. A. **112**:2259 (June 3) 1939.

292. Quick, A. J., and Grossman, A. M.: Prothrombin Concentration in Newborn, Proc. Soc. Exper. Biol. & Med. **41**:227, 1939; Concentration of Prothrombin in Blood of Babies (Three to Seven Days Old), ibid. **40**:647, 1939.

293. Owen, C. A.; Hoffman, G. R.; Ziffren, S. E., and Smith, H. P.: Blood Coagulation During Infancy, Proc. Soc. Exper. Biol. & Med. **41**:181, 1939.

concentration of the blood of newborn infants for six days. They state that their findings, which are opposite to those of Quick, can be explained by the fact that their method estimates prothrombin only, whereas Quick's method does not take into account the conversion time of prothrombin, which is a most important compensating factor. Hellman and Shettles [294] recommend on the basis of their investigations that prothrombin deficiency in premature infants can be prevented by feeding vitamin K to the mother or corrected by administering vitamin K to the infant. Shettles, Delfs and Hellman [295] noted that after administration of vitamin K to the mother the prothrombin level of the infant is about three times the normal. Waddell and his collaborators [296] and Nygaard [297] suggest the use of vitamin K as a preventive and curative measure for hemorrhagic disease of the newborn.

Snell and Butt,[269] in their supplementary report on vitamin K, discuss the possibility that prothrombin deficiency may occur as a result of an inadequate intake of this vitamin. This clinical observation is readily substantiated by the experimental work of Greaves,[298] Murphy [299] and Almquist and Klose,[300] who produced hypothrombinemia in animals after administration of a diet deficient in vitamin K.

Prothrombin deficiency may result from various intestinal disorders, as has been demonstrated by Clark, Dixon, Butt and Snell.[301] Similar observations are noted by Olson;[302] Smith, Ziffren, Owen, Hoffman

294. Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in the Newborn Infant: I. Prematurity and Vitamin K, Bull. Johns Hopkins Hosp. **65**:138, 1939.

295. Shettles, L. B.; Delfs, E., and Hellman, L. M.: Factors Influencing Plasma Prothrombin in the Newborn Infant: II. Antepartum and Neonatal Ingestion of Vitamin K Concentrate, Bull. Johns Hopkins Hosp. **65**:419, 1939.

296. Waddell, W. W., Jr.; Guerry, D., III; Bray, W. E., and Kelley, O. R.: Possible Effects of Vitamin K on Prothrombin and Clotting Time in Newly-Born Infants, Proc. Soc. Exper. Biol. & Med. **40**:432, 1939.

297. Nygaard, K. K.: Prophylactic and Curative Effect of Vitamin K in Hemorrhagic Disease of the Newborn (Hypothrombinemia Hemorrhagica Neonatorum), Acta obst. et gynec. Scandinav. **19**:361, 1939.

298. Greaves, J. D.: Studies on the Vitamin K Requirement of Rats, Am. J. Physiol. **125**:429, 1939.

299. Murphy, R.: Possible Avitaminosis K Produced in Mice by Dietary Means, Science **89**:203, 1939.

300. Almquist, H. J., and Klose, A. A.: Determination of the Anti-Haemorrhagic Vitamin, Biochem. J. **33**:1055, 1939.

301. Clark, R. L., Jr.; Dixon, C. F.; Butt, H. R., and Snell, A. M.: Deficiency of Prothrombin Associated with Various Intestinal Disorders: Its Treatment with the Antihemorrhagic Vitamin (Vitamin K), Proc. Staff Meet., Mayo Clin. **14**: 407, 1939.

302. Olson, P. F.: The Prothrombin Test and the Vitamin K Treatment for the Bleeding Tendency in the Jaundiced Patient, J. Iowa M. Soc. **29**:103, 1939.

and Flynn;[303] Olson and Menzel;[304] Butt, Snell and Osterberg;[305] Stewart;[306] Stewart and Rourke,[307] and Townsend and Mills.[308]

It has been suggested that the liver synthesizes prothrombin and that a hemorrhagic tendency may be associated with severe hepatic damage. Clinically, this is reported by Scanlon and his associates.[309] A similar condition has been produced in hepatectomized dogs by Warren and Rhoads[310] in carefully controlled experiments. Warner[311] also demonstrated the occurrence of hypoprothrombinemia in rats after removal of the liver. A close correlation between prothrombin deficiency and hippuric acid excretion in persons with disease of the liver was observed by Wilson.[312] He suggests that hypoprothrombinemia may be indicative of severe hepatic damage. Wilson and Doan[313] noted a hemorrhagic tendency in rabbits following artifically produced fever and concluded that the bleeding was due not only to decreased platelets but to decreased prothrombin and fibrinogen resulting from severe hepatic necrosis.

Satisfactory treatment for prothrombin deficiency may be accomplished by oral administration of vitamin K. Butt, Snell and Oster-

303. Smith, H. P.; Ziffren, S. E.; Owen, C. A.; Hoffman, G. R., and Flynn, J. E.: The Jaundiced Bleeder: Control of Hemorrhage Through Vitamin K, J. Iowa M. Soc. **29**:377, 1939.

304. Olson, K. B., and Menzel, H.: Bleeding Tendency in Obstructive Jaundice and Its Correction by Means of Vitamin K, Surgery **6**:206, 1939.

305. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: The Preoperative and Postoperative Administration of Vitamin K to Patients Having Jaundice, J. A. M. A. **113**:383 (July 29) 1939.

306. Stewart, J. D.: Prothrombin Deficiency and the Effects of Vitamin K in Obstructive Jaundice and Biliary Fistula, Ann. Surg. **109**:588, 1939.

307. Stewart, J. D., and Rourke, G. M.: Control of Prothrombin Deficiency in Obstructive Jaundice by Use of Vitamin K, J. A. M. A. **113**:2223 (Dec. 16) 1939.

308. Townsend, S. R., and Mills, E. S.: Use of Vitamin K and Bile Salts in Prevention and Control of Hemorrhagic Diathesis in Obstructive Jaundice, Canad. M. A. J. **41**:111, 1939.

309. Scanlon, G. H.; Brinkhous, K. M.; Warner, E. D.; Smith, H. P., and Flynn, J. E.: Plasma Prothrombin and the Bleeding Tendency, with Special Reference to Jaundiced Patients and Vitamin K Therapy, J. A. M. A. **112**:1898 (May 13) 1939.

310. Warren, R., and Rhoads, J. E.: Hepatic Origin of Plasma-Prothrombin Observations After Total Hepatectomy in the Dog, Am. J. M. Sc. **198**:193, 1939.

311. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, J. Exper. Med. **68**:831, 1938.

312. Wilson, S. J.: Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Humans, Proc. Soc. Exper. Biol. & Med. **41**:559, 1939.

313. Wilson, S. J., and Doan, C. A.: Pathogenesis of Hemorrhage in Artificially Produced Fever, Proc. Soc. Exper. Biol. & Med. **41**:115, 1939.

berg [314] report successful results with intravenous administration of phthiocol. Cheney [315] treated chicks with a hemorrhagic tendency by intramuscular injections of vitamin K and concluded that it is a satisfactory and safe procedure. Tage-Hansen [316] compared the oral vitamin K therapy with parenteral methods. In his opinion, intravenous treatment should be given in cases of urgent need; intramuscular treatment has the advantage of prolonged effect but is in reality the poorest type of therapy. Lord and Pastore [317] measured the prothrombin content of "bank" blood and consider it satisfactory for transfusion purposes if stored for less than six to seven days. The prothrombin content of the blood of dogs after transfusions was studied by Lord, Andrus and Moore.[318] A definite increase in prothrombin was noted. The authors conclude that the changes in the prothrombin of the recipient are dependent on the prothrombin content of the plasma of the donor and may be calculated on the basis of addition.

In addition to the vitamin K studies, many interesting observations have been made relative to blood clotting. The characteristics of blood clot formation are described by McKhann and Edsall.[319] Thiberge [320] noted that the blood platelets were reduced in number during allergic attacks and increased during convalescence. If it can be assumed that allergic reactions are associated with increased histamine, the observations of Thiberge are opposite to those of Zon, Ceder and Crigler,[321] who conclude that the histamine content of the blood is dependent on the number of platelets present. Anrep and his associates [322] studied the effect of clotting on the distribution of histamine in the blood. Approxi-

314. Butt, H. R.; Snell, A. M., and Osterberg, A. E.: Phthiocol: Its Therapeutic Effect in the Treatment of Hypoprothrombinemia Associated with Jaundice; a Preliminary Report, Proc. Staff Meet., Mayo Clin. **14**:497, 1939.

315. Cheney, G.: The Intramuscular Injection of Vitamin K, J. Lab. & Clin. Med. **24**:919, 1939.

316. Tage-Hansen, E.: Summary of Some Chemical Studies on Vitamin K, J. A. M. A. **113**:1875 (Nov. 18) 1939.

317. Lord, J. R., Jr., and Pastore, J. B.: Plasma Prothrombin Content of Bank Blood, J. A. M. A. **113**:2231 (Dec. 16) 1939.

318. Lord, J. W., Jr.; Andrus, W. DeW., and Moore, R. A.: Quantitative Study of Effect of Transfusion of Blood on Plasma Prothrombin, Proc. Soc. Exper. Biol. & Med. **41**:98, 1939.

319. McKhann, C. F., and Edsall, G.: Characteristics of Blood Clot Formation, Pennsylvania M. J. **42**:731, 1939.

320. Thiberge, N. F.: The Thrombocyte in Allergy, New Orleans M. & S. J. **91**:372, 1939.

321. Zon, L.; Ceder, E. T., and Crigler, C. W.: The Presence of Histamine in the Platelets of the Rabbit, Pub. Health Rep. **54**:1978, 1939.

322. Anrep, G. V.; Barsoum, G. S.; Talaat, M., and Weininger, E.: Effect of Clotting and of Addition of Histamine on Its Distribution in Blood, J. Physiol. **96**:130, 1939.

mately 50 to 60 per cent of the histamine content of the blood is in the white blood cells. Clotting does not release histamine to the serum.

Volker [323] observed the effect of saliva on coagulation of the blood. Clotting time was readily reduced by the addition of saliva. Neither boiling nor Berkefeld filtration altered the effect of saliva. Putnam and Hoefer [324] performed in vitro and in vivo experiments with cysteine hydrochloride and noted its anticoagulant effects. Similar effects were noted with heparin by Astrup [325] and by Lucia and Aggeler.[326] Milliken [327] and Schumann [328] observed a decreased bleeding time with cessation of bleeding when suitable amounts of oxalic acid were given parenterally to patients.

Copley [329] studied the specificity of thrombin action and points out that it is a catalyst for fibrinogen. Mertz, Seegers and Smith [330] experimented with various amounts of purified thromboplastin, prothrombin and calcium and demonstrated that thrombin itself inactivates prothrombin. Thrombin as a hemostatic agent was investigated by Warner and his associates.[331] These authors recommend it as a suitable coagulant for local application.

Ferguson and Erickson [332] demonstrated that cephalin and calcium increase the clotting power of trypsin, although trypsin alone is active. On the basis of this work and other experiments, these same authors [332] pointed out that the absence of this "clotting enzyme" in the blood of

323. Volker, J. F.: The Effect of Saliva on Blood Coagulation, Am. J. Orthodontics **25**:277, 1939.

324. Putnam, T. J., and Hoefer, P. F. A.: Cysteine Hydrochloride as an Anticoagulant for Clinical Use, Am. J. M. Sc. **198**:502, 1939.

325. Astrup, T.: Heparin and the Inhibition of Blood Clotting, Science **90**: 36, 1939.

326. Lucia, S. P., and Aggeler, P. M.: Heparin and the Blood Coagulation Mechanism, Proc. Soc. Exper. Biol. & Med. **40**:41, 1939.

327. Milliken, L. F.: The Use of a New Blood Coagulant in Transurethral Prostatic Resection, J. Urol. **42**:75, 1939.

328. Schumann, E. A.: Newer Concepts of Blood Coagulation and the Control of Hemorrhage, Am. J. Obst. & Gynec. **38**:1002, 1939.

329. Copley, A. L.: On the Specificity of Thrombin Action, Am. J. Physiol. **126**:310, 1939.

330. Mertz, E. T.; Seegers, W. H., and Smith, H. P.: Inactivation of Prothrombin by Purified Thrombin Solutions, Proc. Soc. Exper. Biol. & Med. **41**:657, 1939.

331. Warner, E. D.; Brinkhous, K. M.; Seegers, W. H., and Smith, H. P.: Further Experience with the Use of Thrombin as a Hemostatic Agent, Proc. Soc. Exper. Biol. & Med. **41**:655, 1939.

332. Ferguson, J. H., and Erickson, B. N.: Calcium and Cephalin in Relation to the Clotting Power of Crystalline Trypsin, Proc. Soc. Exper. Biol. & Med. **40**:625, 1939; A New Clotting Factor and Its Possible Relationship to Hemophilia, Univ. Hosp. Bull., Ann Arbor **5**:45, 1939.

hemophiliacs could well account for the delayed clotting. Brinkhous [333] also studied the clotting defect in hemophilia and concludes that it was the result of delayed thrombin formation.

A most interesting case of abnormal bleeding is described by Schönholzer.[334] The patient was a young boy who since birth had had multiple diffuse recurring hemorrhages. The blood showed a prolonged clotting time. The boy's grandfather died from hemorrhages; one of his sisters had died at the age of 17 days from an umbilical hemorrhage; the blood of another sister, aged 15 years, had a clotting time of twenty-one minutes. Examination of the patient's blood revealed absence of fibrinogen.

BANTI'S SYNDROME

The etiology of splenomegaly has been carefully studied by Rousselot and Thompson.[335] These authors produced progressive hepatic cirrhosis in dogs by multiple intravenous injections of silicious particles over a long period. Microscopically the liver showed definite cirrhotic changes. Studies on the venous pressure of living dogs revealed definite hypertension in the splenic vein. This observation substantiated a previous report by these investigators on the occurrence of hypertension in the lienal vein of patients with so-called Banti's disease. In addition to the aforementioned conditions, the dogs had congestive splenomegaly, anemia and thrombopenia, and in 1 instance esophageal varices were found.

Rousselot [336] reviewed 14 cases of Banti's syndrome. He noted portal stasis and increased venous pressure. The splenomegaly present was secondary to the congestion. There are several factors which may produce congestive splenomegaly. It is most important to know the exact cause of enlargement of the spleen to determine whether it should be removed surgically. In the author's opinion, removal of the spleen should not be attempted if severe disease of the liver is present. In regard to the question of splenectomy, Collins [337] states that the operation may be of some value if performed early in the course of the disease, but the indications are not definite. He also stresses the fact that the spleen should not be removed if portal cirrhosis is present. Splenectomy

333. Brinkhous, K. M.: A Study of the Clotting Defect in Hemophilia: The Delayed Formation of Thrombin, Am. J. M. Sc. **198**:509, 1939.

334. Schönholzer, G.: Die hereditäre Fibrinogenopenie, Deutsches Arch. f. klin. Med. **184**:496, 1939.

335. Rousselot, L. M., and Thompson, W. P.: Experimental Production of Congestive Splenomegaly, Proc. Soc. Exper. Biol. & Med. **40**:705, 1939; The Experimental Production of Congestive Splenomegaly, J. Clin. Investigation **18**: 473, 1939.

336. Rousselot, L. M.: Congestive Splenomegaly (Banti's Syndrome), Bull. New York Acad. Med. **15**:188, 1939.

337. Collins, D. C.: The Value of Splenectomy, West. J. Surg. **46**:628, 1938.

is recommended by Chamberlain [338] at any time, but preferably early in the course of the disease, as the mortality rate increases with the duration of the disease. Jones,[339] in his report on unusual cases of splenic disease, reports an occasional case of Banti's disease in which the patient survived splenectomy. It is difficult to evaluate this paper, as one cannot be sure of the type of case reported.

Andrus and Holman [340] readily admit that Banti's disease does not exist, yet they recommend surgical intervention. They further report a high mortality rate. Hepatic schistosomiasis simulating Banti's disease is reported by Ippolito and Boyd.[341] The patient, a young woman, underwent splenectomy and died. The authors recommended this form of therapy in an effort to prevent the occurrence of degenerative changes in the liver. Schousboe [342] believes that splenomegaly (proliferation of the reticuloendothelial tissue) as observed in Banti's disease inhibits normal erythropoiesis and leukopoiesis. As a result there are anemia, leukopenia, thrombopenia and hyperplasia of the bone marrow. Splenectomy, according to the author, is followed by a return to normal of the hemopoietic functions. Stahr [343] observed 3 cases of splenomegaly associated with syphilis. The patients responded poorly to antisyphilitic therapy; hence splenectomy was performed, with excellent results for one year. Further information concerning the patients was not available.

INFECTIOUS MONONUCLEOSIS

In our previous reviews the historical aspect of infectious mononucleosis was fully discussed. Paul [344] has recently summarized the important clinical features. He states that the disease usually occurs in young adults who live a sedentary life. The presenting symptoms are sore throat, malaise, pain in the shoulders and neck, irregular fever, chilly sensations and enlarged glands. Marshall [345] emphasizes the mental symptoms which may be observed occasionally. The physical signs encountered are enlarged glands, an enlarged spleen, oral lesions, ocular tenderness, puffy eyelids and a maculopapular rash. Spleno-

338. Chamberlain, D.: Surgical Conditions of the Spleen, Clin. J. **68**:182, 1939.

339. Jones, A. P.: Unusual Spleen Cases, Ann. Surg. **109**:960, 1939.

340. Andrus, W. D., and Holman, C. W.: Splenectomy in Various Blood Disorders, Ann. Surg. **109**:64, 1939.

341. Ippolito, T., and Boyd, L. J.: Hepatic Schistosomiasis, Bull. New York M. Coll. **2**:12, 1939.

342. Schousboe, J.: Two Cases of Inhibition of Bone Marrow Due to Splenomegaly, Nord. med. (Hospitalstid.) **2**:1980, 1939.

343. Stahr, G. E.: Splenectomy for Gastric Hemorrhage in Splenomegaly Associated with Syphilis, U. S. Nav. M. Bull. **37**:256, 1939.

344. Paul, J. R.: Infectious Mononucleosis, Bull. New York Acad. Med. **15**: 43, 1939.

345. Marshall, E. A.: Infectious Mononucleosis, Am. J. Clin. Path. **9**:298, 1939.

megaly was present in 50 per cent of the patients examined by Marshall. Templeton and Sutherland [346] observed cutaneous lesions in 18.5 per cent of their series of 91 cases. The eruption was maculopapular, had the appearance of German measles, was usually limited to the trunk and face and was at times associated with pruritus. This rash may appear between the third and the twentieth day; it lasts three to seven days and does not desquamate.

In the early course of the disease leukopenia may be present, and this is followed by leukocytosis. The differential count shows a predominance of characteristic lymphocytes. Bowcock [347] describes blast cells in the peripheral blood and emphasizes the fact that their presence may complicate the diagnosis. The heterophil antibody test, as is pointed out by Paul, gives a positive result in more than 90 per cent of the cases. The temporarily positive Kahn and Wassermann reactions which may often be seen have been the subject of study by Sadusk [348] and Saphir.[349] Sadusk points out that there is no direct correlation between the false positive reactions and the heterophil antibody test. In his opinion the positive Kahn and Wassermann reactions would be seen more frequently if serial tests were done. Saphir emphasizes the fact that the cause of the false positive reactions is not known.

A most interesting observation of the simultaneous occurrence in the same patient of typhoid fever and infectious mononucleosis is reported by Schwartz and Lidman.[350] Since these diseases simulate each other in many respects, the differential diagnosis presented many problems.

The cause of infectious mononucleosis is still the subject of controversy. Pons and Julianelle,[351] in a series of articles, describe the isolation of Listerella monocytogenes, its identification and the immunologic and serologic reactions associated with it. The organism is a small gram-positive rod and grows in small colonies when plated. The organism obtained from the blood, when injected into rabbits, guinea pigs and

346. Templeton, H. J., and Sutherland, R. T.: The Exanthem of Acute Mononucleosis, J. A. M. A. **113**:1215 (Sept. 23) 1939.

347. Bowcock, H.: Mitotic Leukoblasts in the Peripheral Blood in Infectious Mononucleosis, Am. J. M. Sc. **198**:384, 1939.

348. Sadusk, J. F., Jr.: Temporarily Positive Kahn and Wassermann Reactions in Infectious Mononucleosis, J. A. M. A. **112**:1682 (April 29) 1939.

349. Saphir, W.: The Wassermann Reaction in Infectious Mononucleosis, Am. J. Clin. Path. **9**:306, 1939.

350. Schwartz, A. S., and Lidman, B.: Infectious Mononucleosis Complicating Typhoid Fever, Ann. Int. Med. **13**:895, 1939.

351. Pons, C. A., and Julianelle, L. A.: Isolation of Listerella Monocytogenes from Infectious Mononucleosis, Proc. Soc. Exper. Biol. & Med. **40**:360, 1939; Identification of Listerella Monocytogenes, ibid. **40**:362, 1939; Immunological and Serological Reactions of Listerella Monocytogenes, ibid. **40**:364, 1939.

white mice, produced typical lymphocytic-monocytic changes in the blood, and the animals died. When eighteen to twenty-four hour cultures are applied either by instillation or by heavy suspensions into the conjunctival sacs or (by swabbing) on the everted conjunctivas of rabbits, they produce characteristic changes which cannot be elicited or duplicated by any other organism. Antiserums prepared from the various strains which the authors isolated revealed two types, designated I and II. The former was composed of two rabbit and two human strains, and the latter was composed of one strain each from the cow, the sheep and the goat. From their results the authors conclude that immunity to infection is broader than type differentiation as demonstrated by agglutination. Animals with conjunctivitis were immune to similar infections, but intravenous immunization did not offer the same protection.

Wising [352] removed glands from 3 patients with infectious mononucleosis during the febrile stage. Emulsions and, later, antigens were made from this material. No organisms were recognized either microscopically or by cultivation. When these antigens were injected either intracerebrally or intracutaneously into monkeys, fever, enlarged glands and changes in the blood simulating infectious mononucleosis were observed. Emulsions obtained from these glands and injected into other monkeys produced similar results. During the course of these experiments one investigator accidentally inoculated himself, and he subsequently had what the author believes was true infectious mononucleosis.

The prognosis of infectious mononucleosis is good. The disease is self limited and usually runs its full course in two to four weeks. No specific therapy is known. Stannus and Findlay [353] report what they believe is the first case of treatment with sulfapyridine. From all the facts known concerning the disease and the drug, the advisability of general use of the latter for this condition may be questioned.

352. Wising, P. J.: Some Experiments with Lymph Gland Material from Cases of Infectious Mononucleosis, Acta med. Scandinav. **98**:328, 1939.

353. Stannus, H. S., and Findlay, G. M.: Mononucleosis, Acute Infectious: Treatment with Sulfapyridine, Lancet **2**:595, 1939.

(To Be Concluded)

News and Comment

American Congress of Physical Therapy.—The nineteenth annual scientific and clinical session of the American Congress of Physical Therapy will be held Sept. 2-6, 1940, at the Hotel Statler, Cleveland. The mornings will be devoted to an annual instruction and the afternoons and evenings to scientific sessions. There will be symposiums dealing with light, heat and electricity as important therapeutic adjuvants in general medical and surgical practice.

Further information may be procured by writing directly to the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago.

Recently Established Periodicals

Archives balkaniques de médecine chirurgie et leurs spécialités. A quarterly, edited by J. Chryssikos, M. Yoël and A. Hadjigeorges and published by Masson & Cie, Paris, France. The publication of this journal was begun in 1939.

Boletin del Hospital oftalmologico de Ntra. Sra. de la Luz. A bimonthly, edited by Dr. A. Torres Estrada and published by Hospital de Ntra. Sra. de la Luz, Ezequiel Montes, 135, Mexico, D. F. The first issue was for January-February 1940.

Revista cubana de obstetricia y ginecologia. A monthly, edited by Prof. José Ramírez Olivella and published in Habana, Cuba. The first issue was published October 1939.

Revista medica militar. A bimonthly, published by Sanidad Militar in Mexico, D. F. The first issue was published in 1939; the last one in hand covers four months, November and December 1939 and January and February 1940.

Revista mexicana de tuberculosis y enfermedades del aparato respiratorio. A bimonthly, edited by Dr. Donato G. Alarcón and published in Mexico, D. F. The first issue was for July-August 1939.

CORRECTION

In the article by Dr. Francis M. Rackemann entitled "Allergy: A Review of the Literature of 1939," in the January issue (ARCH. INT. MED. **65**:185, 1940), the second sentence of the second paragraph on page 199 should read: "Of 83 consecutive asthmatic patients who were subjected to bronchoscopy at the Clinic, 33 patients (40 per cent) were found to have definite stenosis of one or, occasionally, more of the bronchi."

Book Reviews

Die Eiweisskörper des Blutplasmas. By H. Bennhold, E. Kylin and St. Rusznyák. Price, 40 marks. Pp. 476, with 59 illustrations. Dresden: Theodor Steinkopff, 1938.

The book is a collection and synthetic evaluation of the dispersed accumulation of data concerning the proteins of the blood plasma. It has two main divisions: a general and a clinical one. In reviewing a new venture such as this one, it may be best to furnish the reader an idea of the scope of the undertaking by enumerating the chapters and the names of the writers thereof, all of whom have been prominent workers in their respective fields.

The first chapter of the general section, by R. E. Liesegang, deals with fundamental physicochemical conceptions. One of the main features of the whole book becomes evident in this chapter: The preponderant consideration of the physicochemical aspects of the problem. A chapter with a more comprehensive treatment of the chemistry of the plasma proteins might not be an unwelcome addition to this book.

In the second chapter E. Kylin considers the fundamental physiologic conceptions of the plasma proteins. Here, as in other chapters, it is stressed that the methods of separating the various protein fractions usually alter the proteins as they occur in the blood, although it is not denied that much useful information has been obtained by the employment of such methods. The newer methods of identification by means of the ultracentrifuge and by cataphoresis constitute an advance in this direction. However, it would seem rather difficult to decide anything as to the occurrence of different kinds of fibrinogen, for instance, and their possible functions in vivo by cataphoretic experiments with a plasma of a p_H as high as 12.4. From analogy, it would be expected that at such a degree of alkalinity ammonia would be liberated from protein, producing changes even greater than those obtained by salting out.

In the third chapter, Jürgens discusses the origin of the plasma proteins. He favors the view that they originate where the formed elements of the blood are produced. He emphatically states that the liver cannot be regarded as the sole source of any of the plasma proteins.

In the fourth chapter, Hatz provides a critical review of various methods of determination of the blood proteins. In the fifth, Geill treats of the precipitation of the blood proteins by means of the salts of the light and heavy metals. It is justly stressed that the complete reversibility of the precipitation with the light metal salts can be expected only when a number of conditions are realized. Enlargement of the chapter, particularly with regard to the precipitation by other agents, such as alcohol and acetone, which when employed under proper conditions yield soluble precipitates, may not be amiss.

The sixth chapter, "The Colloid Pressure of the Blood," has been entrusted to von Farkas, who prefers the term "colloid pressure of the blood" to "colloid osmotic pressure" or "oncotic pressure." Needless to say, this chapter contains much of great interest. The more surprising it is that the "*Leberspere*" in man is accepted as if no very weighty objection to it had ever been raised. It is also stated that Nonnenbruch calls attention to the fact that even the capillaries of the extremities are entirely impermeable to protein. The work of Drinker and his co-workers, dealing with this subject, deserves some consideration and more than it has received in other chapters of this book. The writer of this chapter thinks that a neurohormonal regulation of the colloid pressure may be assumed to exist, though its existence is not yet proved. As in a later chapter by Rusznyak, the importance of water and sodium chloride for the production of edema is stressed by von Farkas.

In the seventh chapter, Bennhold treats of the transporting function of the blood proteins. This function of the blood proteins, to the knowledge of which Bennhold has contributed so much, has not yet received the consideration it demands from the physician, so it may be well to call attention briefly to the "embatic" effect. A coarsely dispersed acid dye (such as, for instance, Congo red) in watery solution, placed over a 5 per cent gelatin gel, does not penetrate into the gel; whereas, when it is added to serum it does penetrate into the gel as far as the serum albumin.

Furthermore, various substances—the regular constituents of the organism, such as bilirubin or bodies foreign to it—travel in the electric field, some with the albumin and some with the globulin fractions and others free. The results are summarized in a table. More or less firm combinations with the proteins may be formed, and the substances may be unloaded in different organs, whereby different forces may exert themselves. An exception may be taken to the fact that the author calls the structural chemical difference between coproporphyrin and uroporphyrin a minimal one. The first attaches itself to albumin and the latter does not, but there is a difference of four carbonyl groups in favor of uroporphyrin, as given in the formulas. Without detracting from the other contributors, this particular chapter is perhaps the most stimulating one of the book. It forms the concluding chapter of the general section, which comprises 303 of the 470 pages of the book.

The first chapter of the clinical section of the book gives the normal and pathologic limits of the proteins as compiled by Hath and Koranyi, with the methods of their determination. The second chapter of this section deals with the relation of the plasma proteins to edema. Here Rusznyak emphasizes the importance of the diminished colloid osmotic pressure in addition to that of the venous pressure. Thus, for instance, in the presence of cardiac edemas the colloid osmotic pressure is normal but the venous pressure is high; whereas in the nephrotic type of edema the colloid osmotic pressure is low, and the venous pressure is normal.

In chapter 3 the relation of the plasma proteins to albuminuria is discussed by Koranyi. The conclusion is reached that albuminuria in cases of renal disease, as well as in febrile conditions, is due to an increased permeability of the glomerulus and not to a pathologic change in the plasma proteins. The normal glomerulus passes proteins of less than 70,000 molecular weight, and the diseased glomerulus does this more readily.

In the fourth chapter the relation of serum protein to serologic reactions is discussed by Klinke. The subject also is treated mainly from the colloid chemical standpoint, with little reference to the clinical aspect. This deficiency, it may be stated here, is shared with the other chapters of this section.

In the fifth chapter, Kylin gives pathologic protein reactions to the blood. Here the sedimentation rate of the red blood corpuscles is discussed. The relation to fibrinogen and to the globulins is shown, and it is pointed out that with an increase in these proteins the sedimentation rate increases to a greater extent than does the concentration of the proteins. For the clinical evaluation of the sedimentation rate, the reader is referred to the book of Reichel. The Takata test, the "formol-gel" test and other tests also are treated from the standpoint of their relation to the proteins rather than from that of their clinical applications.

The sixth chapter, by Klinke, on plasma protein and the coagulation of blood, concerns itself with the mechanism of the coagulation and retraction of the clot.

In the seventh, and last, chapter, a summary of the significance of the plasma protein in its clinical application is attempted by Kylin. The discussion is based on the conception that the plasma proteins are to be considered as an organ, a conception first advanced by Bennhold. Thus, for instance, a subheading is "The Diseases of the Organ of the Plasma Proteins." With reference to the red blood corpuscles the distinctions are (1) too few red blood cells (anemia), (2) too many red blood cells (polyglobulic)) and (3) a pathologic form of red blood cells (poikilocytosis) in which 1 and 3 are often combined.

With reference to the white blood cells we have (1) too few white blood cells (leukopenia), (2) too many white blood cells (leukemia) and (3) a pathologic form of white blood cells (2 and 3 are often combined).

With reference to the plasma proteins there are (1) diseases with hypoproteinemia (hypofibrinogenemia, hypoglobulinemia and hypoalbuminemia), (2) diseases with hyperproteinemia (hyperfibrinogenemia, hyperglobulinemia and hyperalbuminemia) and (3) diseases with pathologic plasma proteins.

The conception of the plasma proteins as an organ is justified on the contention that an organ is a part of the body having a special function. However, according to this definition, connective tissue would be an organ, as also would peripheral nerves and other structures. Whether the conception of the plasma proteins as an organ in this sense will find favor is questionable. Here it may be sufficient to state that the book has succeeded in its main purpose, which is to give a somewhat organic connection to more or less isolated facts. The book is stimulating and is certainly to be recommended to the physician who does not demand an immediate, clearcut application in his everyday practice.

Anemia in Practice. By William P. Murphy, A.B., M.D. Price, $5.00, cloth. Pp. 344, with 46 illustrations. Philadelphia: W. B. Saunders Company, 1939.

In the preface Murphy states: "For several years it has been my desire to assemble the vital information concerning the anemias which is now at hand." Paraphrasing this quotation, there has been a great deal of productivity in the field of hematology in the last fifteen years, which has resulted in a great increment to the knowledge of the anemias. This is particularly true of pernicious anemia. The author is responsible for a goodly part of the information that has been obtained. Because of his intensive work in the problems of anemia and because of his large clinical experience, Murphy is well equipped to prepare this monograph. It need hardly be added that on account of the author's interest in pernicious anemia the book is almost entirely devoted to this particular type of blood dyscrasia. Illustrating this statement is the fact that part 1, some 64 pages, is devoted to the classification and diagnosis of the hypochromic anemias and their treatment and to the normocytic anemias and their treatment; whereas part 2, which has to do with pernicious anemia, is some 200 pages in length.

The section devoted to pernicious anemia first devotes a few pages to the historic aspects of the disease. Then it deals with the diagnosis. Murphy then discusses the mechanism of red cell formation under normal and abnormal circumstances. To liver therapy are devoted four chapters. Succeeding chapters have to do with the prognosis, incidence, complications, differential diagnosis and practical management of the patient. The last 50 pages of the book dwell on laboratory procedures and blood transfusion.

Only a few comments seem appropriate. Murphy is so familiar with his subject from personal observation and has so thoroughly covered the literature that little can be added. Certainly nothing unfavorable can or need be said concerning the subject matter of this book in so far as it applies to pernicious anemia. On the other hand, the discussion of anemias other than pernicious anemia seems to be quite sketchy and somewhat inadequate.

I am glad to find that Murphy believes in the use of the hematocrit but confines hematocrit studies to determining the mean corpuscular volume of the red cells, the simplest method of determining increase in the size of the cells. He implies that in the absence of achlorhydria the diagnosis of pernicious anemia may well be questioned. He believes that the parenteral administration of liver is the therapy of choice and that the patient should continually receive a maintenance dose with the minimum amount of difficulty or trouble.

It hardly seems appropriate to put in a book which represents so much deep scientific thought and remarkable series of clinical studies, illustrations which would appeal to the mind of a 10 year old child. To see little one-lined men pouring material into a stomach certainly does not attribute much intelligence to the reader.

Principles of Hematology with 100 Illustrative Cases. By Russell L. Haden, M.A., M.D. Price, $4.50, cloth. Pp. 348, with 155 illustrations. Philadelphia: Lea & Febiger, 1939.

In this monograph Haden discusses first the formation of blood, taking up the embryologic as well as the physiologic considerations in some detail. Succeeding chapters have to do with the leukocytes, the thrombocytes and the technic of examination of the blood. The next three chapters dwell on the mechanism of production of various abnormalities of the blood, the word "abnormalities" being used in its broader sense. The explanation of the mechanism of leukocytosis and leukopenia, for example, is most interesting and informative. Treatment of the hematic disorders then follows. This completes the formal presentation of the subject of hematology.

The remaining eleven chapters are particularly to be commended. In them, approximately one third of the book, is a series of case reports covering succinctly and clearly all the various types of anemia, such as polycythemias, leukocytoses and leukemias. This section makes interesting reading and explains clearly the rather dogmatic, didactic first two thirds of the book.

The book is well illustrated with photomicrographs. It is one of the pleasant features of the volume that there are no colored plates of the blood, which are so frequently poorly reproduced and inaccurately colored. There is a wealth of diagrams which add materially to the understanding of the printed word. These may seem rather elementary, but to the student or to a man who is not primarily interested in hematology they will be of inestimable value.

Haden, like most present day clinical hematologists, stresses the importance of hematocrit readings in the study of disorders of the blood. Some of the more complicated formulas that he has devised are mentioned, but, as reflected in the case reports, most of them are discarded after the primary description of how to obtain them and what they imply. The mean cell volume, the most important observation of the hematocrit reading, is not neglected.

The book is to be recommended most highly. Unless one is thoroughly familiar with hematology it will prove of great everyday service to the man who is coming in contact with patients suffering from hematologic disorders, and nearly every person who is sick does have some disturbance of the red cells, of the hemoglobin, of the white cells or even of the thrombocytes.

Classic Descriptions of Disease. Ralph H. Major, M.D., Professor of Medicine, The University of Kansas. Second Edition. Price, 5.50. Pp. 727. Springfield, Ill., and Baltimore: Charles C. Thomas, Publisher, 1938.

In this book four hundred original accounts of disease are presented in English with pertinent material relative to the history of the disease and brief biographies of the various authors. For example, when dealing with diabetes mellitus Major selects the following accounts: that of the Papyrus Ebers (1500 B. C.), the fascinating descriptions of Aretaeus (second century A. D.), the article of Willis (dealing with the sweet taste of the urine), Kussmaul's account of air hunger and diabetic coma, Mering and Minkowski's observations on the production of experimental diabetes by pancreatectomy, Opie's description of the hyaline degeneration of the islets of Langerhans and finally the announcement of Banting and Best of the successful extraction of the internal secretion of the pancreas from degenerated pancreatic tissue. There are sections dealing with infectious diseases, metabolic diseases, lead poisoning, diseases of the circulatory system, diseases of the blood, kidney disease, respiratory diseases, deficiency diseases, allergic diseases and dieases of the digestive tract. For obvious reasons, in the compilation of such an anthology not all the diseases selected could be presented completely or dramatically. In the selection of his material Major tried to choose "either the first known, one of the earliest or one of the most interesting accounts of the disease

in question." No attempt was made to consider all diseases with equal completeness, "since some diseases have more interesting and more extended histories than others and also because of personal taste, or bias if you will, in the selection of authors."

In the preparation of this work Major had in mind the value of approaching the history of medicine from the clinician's point of view. Thus, he begins with a disease and leads the reader back to the various personalities that contributed to our knowledge of it, instead of introducing a famous character and commenting on the various diseases that the savant happened to be interested in. Consequently, the book helps bridge the gap between the cursory history of diseases that is given in the ordinary history of medicine and the formal histories of medicine that are predominantly biographic.

Technically, the standard of printing is high. The book is easily handled and will make a valuable addition to the library of any one directly or even remotely interested in medicine.

The second edition has been improved by the addition of material on yellow fever and malaria, the revision of various biographic sketches and the incorporation of additional readings and illustrations.

Menstrual Disorders: Pathology, Diagnosis and Treatment. By C. Frederic Fluhmann, M.D., C.M. Pp. 329, with 119 illustrations. Philadelphia: W. B. Saunders Company, 1939. Price, $5.

In this excellent volume is presented not only a fine discussion of menstrual disorders but a minute, concise description of the normal menstrual cycle. The intricate interrelationships of the hormones concerned in menstruation and the results of disturbed mechanism of these hormones as reflected in uterine bleeding are discussed in detail and presented clearly and comprehensively. The author's classification of menstrual disorders and abnormal uterine hemorrhage is excellent and serves as a good working basis for clinical diagnosis. The chapter on dysmenorrhea is particularly recommended. Bleeding as a result of pathologic pelvic conditions is discussed remarkably well, and the reasons for the bleeding associated with these conditions are clearly explained from the viewpoint of both pathologic findings and pathologic function.

The value of this book is enhanced by the abundance of excellent photomicrographs and charts, the majority of the latter being original.

This volume contains a wealth of information and should prove of immeasurable value not only to the gynecologist but to any one who is concerned with the care of female patients. The style and composition are such as to make the book easily understandable to the average medical student.

Short Stature and Height Increase. By C. J. Gerling. Price, $3.00. Pp. 159. New York: Harvest House, 1939.

This book, written for the laity, is motivated by the thesis that the person who happens to be of short height is unfortunate in his contacts with other people. The author points out that the big man has the advantage in more ways than one over the short man. Furthermore, the short person feels that he is at a disadvantage and often is truculent and self assertive. The purpose of the book is to sketch how the person may overcome the handicap of short stature. Gerling suggests measures which may have some effect on the height of the adult. Although there is little that can be done to increase height, by maintaining a good posture, which is built up by exercises, the short person is able to take care of his defect to a certain extent. Also, such customs as wearing garments which give the appearance of height, elevating the heels of the shoes, avoiding smoking large cigars and pipes and wearing a mustache may give a certain amount of spurious increase in height which would be of psychologic help to the small man.

The book is written in an attractive style and should be of great interest to the short person. The advice for the most part is sane, sensible and easy to follow. The doctor may cause gratitude in the heart of his patient small in stature if he recommends the book to him.

The Patient as a Person: A Study of the Social Aspects of Illness. By George Canby Robinson. Price, $3.00. Pp. 423. New York: Commonwealth Fund, Division of Publications, 1939.

Dr. Robinson has written an interesting book which I hope will be widely read and will do some good. In these days when there is great effort to make diagnoses purely from laboratory and roentgenologic reports, there is much need for protesting books like this which show how often a serious situational neurosis complicates organic disease and perhaps makes successful treatment impossible. This is probably particularly true in the case of clinic patients, but it is almost as true of patients of the middle and upper economic classes, who are commonly unhappy, worried, overworked or psychopathic.

The book is made up almost entirely of well abstracted case reports in which only essential points are given. It should be read by all young physicians starting out in practice, and it should of course be read by all students who plan to be social service workers.

The Physiology and Pharmacology of the Pituitary Body. Volume II. By H. B. Van Dyke, M.D. Price, $4.50. Pp. xiv + 402, with 28 illustrations and 10 tables. Chicago: University of Chicago Press, 1939.

The first volume of this book was published in 1936 and was reviewed favorably in the Archives of Internal Medicine (**60**:248 [Nov.] 1937)). The second volume also deserves much praise. It continues with a critical review of the history of research on the pituitary body from 1935 until 1938 and represents a sifting and classifying of all recent work on the physiology and pharmacology of this peculiar gland. The bibliography contains 1,418 titles, which the author states represent only 78 per cent of the articles which were considered.

Inevitably, the two volumes together will prove of great usefulness to all students, investigators and clinicians who have any interest in modern endocrinology.

Landmarks in Medicine. By various authors, with an introduction by James Alexander Miller, President, New York Academy of Medicine. Price, $2.00. Pp. 347 with 15 illustrations. New York: D. Appleton-Century Company, Inc., 1939.

This is one of the series of books promoted by the New York Academy of Medicine and containing lay lectures on medical subjects. These books are most interesting and valuable from a historical point of view and in addition make delighful reading. It is difficult to place one lecture above another in interest and value, but it is worth a wager that the majority of readers will turn first to Martland's "Dr. Watson and Mr. Holmes." Other contributors are Francis R. Packard, Alfred E. Cohn, James J. Walsh, Raymond Pearl, Reginald Burbank and Lewis Gregory Cole.

Les cholécystites chroniques. By A. Danès. Préface de J. Rieux. Price, 38 francs, paper. Pp. 118, with 11 illustrations. Paris: Gaston Doin & Cie, 1937.

This is a brief monograph on chronic cholecystitis. It is entirely a clinical study and largely nontheoretic, and is presented as "a practical guide for the general practitioner." The author reviews clearly the more elaborate experimental contributions that have been made in the field it covers, particularly in the study of the diseased gallbladder, and translates these studies into simpler observations,

which can be made at the bedside for the most part. The book will be of interest to those who read French and will prove instructive to those who are primarily interested in disease of the gallbladder, be they surgeons or internists.

Herz-und Kreislauferkrankungen in ihren Beziehungen zum Nervensystem und zur Psyche. By H. D. von Witzleben. Price 4.50 marks. Pp. 101. Leipzig: Georg Thieme, 1939.

This little book consists in essence of a review of the physiology of the circulation, with comments on abnormal conditions, such as hypertension. However, with hypertension, for example, there is no thorough discussion of current views as to humoral pressor substances. In general, moreover, the book lacks adequate documentation. There are no references and no index. It is, however, well written and makes interesting and stimulating reading.

Epidemic Encephalitis. Third report by the Matheson Commission (Willard C. Rappelye, Chairman). Price, $3. Pp. 493, with 33 tables and 4 charts. New York: Columbia University Press, 1939.

This critical and authoritative summary of the problem of encephalitis is a timely contribution to a subject important to all physicians. The bibliography, occupying nearly three hundred pages, is in itself a valuable piece of work. Current theories on causes of the various types of encephalitis, treatment and epidemiology are all discussed, with the aid of many pertinent tables and charts.

Harvey Cushing's Seventieth Birthday Party. By the Harvey Cushing Society. Price $3.00. Pp. 146, with 9 illustrations. Springfield, Ill.: Charles C. Thomas, 1939.

There is in existence a Harvey Cushing Society comprised of some 47 active members: a group of men interested in various aspects of neurosurgery scattered all the way from New Orleans to Toronto, from San Francisco to Boston, and with corresponding members in Breslau, Manchester, Oxford, Paris and Stockholm. It is a lively little club, each member owing something of his accomplishments and ideals to Harvey Cushing. Thus, when this society held its eighth annual meeting in New Haven last April to celebrate Dr. Cushing's seventieth birthday, the occasion was not without significance. There were speeches and the drinking of healths; tributes, telegrams and letters from members who could not be there, and even more telegrams and letters from nonmembers who wished they were of the elect. On the whole, the occasion was a joyish one with a good deal of merriment.

This birthday party now has been perpetuated in book form. It is a gay, friendly little volume. Even from the pictures of the occasion one catches glimpses of Dr. Cushing's vitality. His own speech, of course, is characteristically graceful and charming. Graduates of the Hospital—to the alumni of Massachusetts General Hospital there can ever be but one Hospital—will enjoy the account of Dr. Cushing's career as "house pupil." This has been carefully described by Dr. Henry R. Viets with some interesting reproductions of the manner in which, even in those early days, Dr. Cushing kept his clinical records.

It does no harm to emphasize the human side of a great doctor. Dr. Cushing's friends as well as future medical historians will be glad of this unusual sidelight on his career.

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